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# EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

## IX. BLOOD PLASMA PROTEIN VALUES FOR CONTROL AND PARTIALLY NEPHRECTOMIZED RATS FED DIETS CONTAINING DRIED EXTRACTED BEEF MUSCLE

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Hypoproteinemia may follow excessive loss or deprivation of protein. Experimental hypoproteinemia has been produced by plasmapheresis and with diets low in protein. In man, hypoproteinemia is encountered after continued loss of protein in urine or during periods of dietary restriction of protein. Many investigators believe that the hypoproteinemia is entirely due to this loss of protein. However, in a recent discussion of the problem, Bloomfield [1] suggested: "Part at least of the difficulty which leads to the lowering of the blood-proteins is an impairment of the blood-regenerating mechanism; lack and loss undoubtedly contribute an added burden which on occasion may be insuperable, but lack and loss clearly fail to explain the whole problem."

In the present investigation, control and partially nephrectomized rats fed diets containing varying amounts of dried extracted beef muscle were used in studying the relation between the plasma protein content and the amount of protein ingested and excreted. The partially nephrectomized rat is peculiarly suitable for such a study for the following reasons: 1. The urinary protein is chiefly albumin in proportions found in nephrotic urine of man. 2. The severity of the proteinuria increases with time. 3. The amount of dietary protein influences the excretion of protein to a certain extent. Despite the marked loss of protein by partially nephrectomized rats, neither hypoproteinemia nor visible edema was encountered.

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This investigation was made possible by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.

1. Bloomfield, A. L.: The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, J. Exper. Med. **57**:705, 1933.

## METHODS

The operative procedure for unilateral and subtotal nephrectomy and the care of the experimental animals have been described.[2] The diets are presented in table 1. The control and partially nephrectomized rats were fed the experimental diets for periods ranging from seventy-five to one hundred and fifty days, with about one hundred days for the majority of animals.

Blood for analysis of protein was drawn from the abdominal aorta with needle and syringe while the animal was under light ether anesthesia. Potassium oxalate was used as the anticoagulant. An effort was made to use uniform concentration of potassium oxalate in order to minimize the analytic error pointed out by Peters, Eisenman and Bulger.[3] The procedure described by Weech, Snelling and Goetsch [4] was followed for the determination of total plasma, albumin and fibrin nitrogen. Globulin was precipitated with 22.2 per cent solution of sodium sulfate after incubation overnight, and the solution was filtered through a Whatman no. 50 filter paper. Fibrin was prepared for analysis according to the Cullen and Van Slyke [5] method from 1 cc. of plasma. The micro-Kjeldahl apparatus was similar to Goebel's apparatus, described by Peters and Van Slyke.[6] The nonprotein nitrogen content was determined by the procedure suggested by Daly.[7] The blood

TABLE 1.—*Composition of Rations*

| Diet | Dried Extracted Beef Muscle | Starch | Lard | Cod Liver Oil | Dried Yeast | Salt Mixture |
|---|---|---|---|---|---|---|
| EB 10 | 10 | 62 | 14 | 5 | 5 | 4 |
| EB 20 | 20 | 52 | 14 | 5 | 5 | 4 |
| EB 40 | 40 | 32 | 14 | 5 | 5 | 4 |
| EB 60 | 60 | 12 | 14 | 5 | 5 | 4 |
| EB 80 | 80 | .. | 6 | 5 | 5 | 4 |

filtrate was prepared in a centrifuge tube by adding 0.2 cc. of plasma to 5 cc. of 2.5 per cent trichloro-acetic acid. Slightly more than 3 cc. of plasma was necessary for the determination of total plasma protein, albumin, globulin and nonprotein nitrogen. Since sufficient plasma was not always available to include analysis of fibrin, this determination alone was made for a number of other animals to obtain sufficient data. The urinary protein content was determined for urine collected during a concentration test according to the procedure of Folin.[8]

2. Chanutin, A. and Ferris, E. B., Jr.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: I. Control Diet, Arch. Int. Med. **49**:767 (May) 1932.

3. Peters, J. P.; Eisenman, A. J., and Bulger, H. A.: The Plasma Proteins in Relation to Blood Hydration: I. In Normal Individuals and in Miscellaneous Conditions, J. Clin. Investigation **1**:435, 1925.

4. Weech, A. A.; Snelling, C. E., and Goetsch, E.: The Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on a Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis, J. Clin. Investigation **12**:193, 1933.

5. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 697.

6. Peters and Van Slyke,[5] p. 530.

7. Daly, C. A.: The Determination of Non-Protein Nitrogen with Special Reference to the Koch-McMeekin Method, J. Lab. & Clin. Med. **18**:1279, 1933.

8. Folin, O.: A Laboratory Manual of Biological Chemistry, New York, D. Appleton and Company, 1926, p. 210.

The standard error of the mean and the coefficient for reliability between two means were determined according to formulas recommended by Garrett.[9]

## RESULTS

*Plasma Protein Values for Control Animals (One or Two Kidneys).*—The total protein, albumin and globulin nitrogen concentrations were determined for 97 control animals fed diets containing 10, 20, 40, 60 or 80 per cent dried extracted beef muscle. The average values with their standard errors are presented in the first portion of table 2. The respective mean values for the total plasma protein and albumin were practically the same with the first four diets, but there was a statistically significant difference for these constituents for the groups fed the

TABLE 2.—*Plasma Protein Values for Control and Partially Nephrectomized Rats*

| | | Total | | Albumin | | Globulin | | Fibrin* | |
|---|---|---|---|---|---|---|---|---|---|
| No. of Rats | Protein in Diet, % | Nitrogen, Mg. per 100 Cc. | Protein, Gm. per 100 Cc. | Nitrogen, Mg. per 100 Cc. | Protein, Gm. per 100 Cc. | Nitrogen, Mg. per 100 Cc. | Protein, Gm. per 100 Cc. | Nitrogen, Mg. per 100 Cc. | Protein, Gm. per 100 Cc. |
| | | | | Control Rats | | | | | |
| 17 | 10 | 1,001 ± 10.7 | 6.25 | 562 ± 9.3 | 3.51 | 439 ± 15.8 | 2.74 | 44 ± 1.6 | 0.28 (18) |
| 14 | 20 | 995 ± 14.3 | 6.23 | 552 ± 12.0 | 3.45 | 443 ± 9.4 | 2.77 | 47 ± 1.3 | 0.29 (26) |
| 14 | 40 | 988 ± 11.1 | 6.17 | 531 ± 8.3 | 3.32 | 457 ± 12.8 | 2.86 | 45 ± 2.5 | 0.28 (19) |
| 21 | 60 | 1,000 ± 15.3 | 6.25 | 550 ± 6.3 | 3.44 | 450 ± 13.1 | 2.82 | 42 ± 1.4 | 0.26 (21) |
| 31 | 80 | 952 ± 9.4 | 5.95 | 505 ± 5.8 | 3.16 | 447 ± 9.9 | 2.80 | 46 ± 1.9 | 0.29 (12) |
| | | | | Partially Nephrectomized Rats | | | | | |
| 38 | 10 | 988 ± 16.4 | 6.17 | 522 ± 13.4 | 3.26 | 466 ± 17.7 | 2.91 | 46 ± 2.0 | 0.29 (24) |
| 24 | 20 | 938 ± 19.2 | 5.86 | 503 ± 13.1 | 3.14 | 435 ± 15.5 | 2.72 | 50 ± 2.5 | 0.31 (19) |
| 19 | 40 | 935 ± 12.0 | 5.84 | 465 ± 11.5 | 2.91 | 470 ± 13.4 | 2.94 | 59 ± 3.0 | 0.37 (20) |
| 24 | 60 | 955 ± 14.6 | 5.97 | 478 ± 11.6 | 2.99 | 477 ± 12.0 | 2.98 | 52 ± 3.2 | 0.33 (18) |
| 26 | 80 | 928 ± 13.8 | 5.80 | 457 ± 11.3 | 2.86 | 471 ± 18.8 | 2.94 | 70 ± 3.6 | 0.44 (30) |

* The figures in parentheses represent the number of rats used for determinations of fibrin.

EB 80 diet. The average globulin and fibrin values were all within a small limited range with all diets and were without any statistically significant differences.

Since the mean values for the groups fed diets EB 10, EB 20, EB 40 and EB 60 were statistically reliable, they were combined with maximum and minimum values to establish standards for control rats fed well balanced diets (table 3).

*Plasma Protein Values for Partially Nephrectomized Rats.*—The total plasma protein, albumin and globulin nitrogen concentrations were determined for 133 partially nephrectomized rats fed diets containing 10, 20, 40, 60 or 80 per cent dried extracted beef muscle. The statistical

9. Garrett, H. E.: Statistics in Psychology and Education, New York, Longmans, Green & Co., 1930.

analysis of the average values for each dietary group is presented in the second portion of table 2. There was a tendency for the concentrations of total plasma protein and albumin to decrease slightly as the protein concentration of the diet was increased. There was a statistically significant difference between the total plasma protein content with diet EB 10 and the values with the remaining diets. There was a significant difference between the albumin values with diets EB 10 and EB 20, respectively, and the values with diets EB 40, EB 60 and EB 80, respectively. There was no significant difference between the globulin values, despite the fact that the spread about the mean was greatest for this constituent. The maximum and minimum values for the various plasma constituents were as follows: total protein nitrogen, 1,192 and 800 mg.

TABLE 3.—*Plasma Protein Values for Control Rats*

| Number of Rats | | Mg. of Nitrogen in 100 Cc. of Plasma | Gm. of Protein in 100 Cc. of Plasma |
|---|---|---|---|
| 66 | Total | Maximum 1,180<br>Minimum 860<br>Mean 1,001 ± 7.0 | 6.25 |
| | Albumin | Maximum 653<br>Minimum 465<br>Mean 548 ± 4.6 | 3.42 |
| | Globulin | Maximum 592<br>Minimum 278<br>Mean 453 ± 6.6 | 2.83 |
| | $\frac{\text{Albumin}}{\text{Globulin}}$ ratio = 1.21 | | |
| | Correlation coefficient between albumin and globulin = −0.14 ± 0.08 | | |
| 96 | Fibrin | Maximum 0.069<br>Minimum 0.029<br>Mean 0.045 ± 9.0 | 0.28 |

per hundred cubic centimeters; albumin nitrogen, 668 and 320 mg. per hundred cubic centimeters, and globulin nitrogen, 757 and 257 mg. per hundred cubic centimeters.

The average values for fibrin showed an increase in concentration with increased ingestion of protein. It should be noted that these increased values were not sufficient to influence the globulin values appreciably. The maximum and minimum variations for fibrin nitrogen for the partially nephrectomized rats were 106 and 28 mg. per hundred cubic centimeters, respectively.

*Comparison of Plasma Protein Values for Control and Partially Nephrectomized Rats.*—The data for the total plasma protein, albumin and globulin were statistically analyzed to determine the effect of partial nephrectomy for the respective dietary groups. It was found that there was no significant difference in the average values for total nitrogen for the groups of animals fed diets EB 10 and EB 80, but there was a significant difference for the groups fed diets EB 20, EB 40 and

EB 60. There was a significant difference between the average albumin values for all the respective dietary groups. On the other hand, there was no significant difference in the average globulin values for the various dietary groups. The values for fibrin were significantly greater for the partially nephrectomized animals fed diets EB 40, EB 60 and EB 80 than for the corresponding control groups. It should be emphasized that the absolute decrease in the values for total plasma protein and albumin was not physiologically significant.

*Relation of Plasma Protein Values to Urinary Protein Values for Partially Nephrectomized Rats.*—In order to determine whether the concentration of plasma protein was related to the amount of protein excreted, all data were assembled under arbitrary ranges of proteinuria according to the amount of protein excreted in twenty-four hours, as follows: group 1 (slight proteinuria), between 0 and 50 mg.; group 2 (moderate proteinuria), between 50 and 100 mg., and group 3 (marked

TABLE 4.—*Relation of Proteinuria to Plasma Protein Values for Partially Nephrectomized Rats*

| Group | Number of Rats | Mg. of Protein Excreted in 24 Hr.* | Gm. of Protein in 100 Cc. of Plasma | | |
|---|---|---|---|---|---|
| | | | Total | Albumin | Globulin |
| 1..... | 38 | 0- 50 (28) | 6.13 ± 0.24 | 3.17 ± 0.33 | 2.98 ± 0.45 |
| 2..... | 28 | 50-100 (72) | 5.91 ± 0.41 | 3.03 ± 0.33 | 2.89 ± 0.37 |
| 3..... | 37 | 100-250 (145) | 5.75 ± 0.36 | 2.93 ± 0.38 | 2.82 ± 0.40 |

* The figures in parentheses represent averages.

or massive proteinuria), between 100 and 250 mg. The average values for plasma protein, albumin and globulin are classified according to the proteinuria in table 4.

Since the differences in the concentration of the plasma protein for the respective groups were comparatively small, statistical analyses for the significance of the differences of the averages were carried out. It was found that the average values for total plasma protein for groups 2 and 3 were definitely lower than the average value for group 1. There was a significant difference between the albumin values for group 1 and those for group 3. There were no appreciable differences in the globulin values for the three groups. Although there were statistically significant differences between the groups with regard to the total plasma protein and albumin values, it can be seen that the plasma protein concentration was not sufficiently lowered to exert any untoward physiologic effect.

The quantity of circulating plasma protein in 101 partially nephrectomized rats, which was estimated from the total plasma protein con-

centration and the plasma volume (method of Cutting and Cutter[10]), was compared with the urinary protein excreted during a twenty-four hour concentration test. Thirty per cent of these animals excreted more than 50 per cent of the calculated total plasma protein in twenty-four hours. In two instances the twenty-four hour urinary excretion of protein was in excess of the calculated total plasma protein content. In the absence of hypoproteinemia this demonstrated a remarkable ability of the partially nephrectomized rat to regenerate plasma protein.

## COMMENT

These experiments demonstrate that tremendous increases in the protein concentration of an adequate diet do not increase the plasma protein content for control and partially nephrectomized rats. Furthermore, the loss of relatively large quantities of urinary protein by partially nephrectomized rats has no appreciable effect on the concentration of plasma protein. This appears to be direct experimental evidence to support Bloomfield's suggestion that loss of urinary protein in renal disease does not satisfactorily explain the phenomenon of hypoproteinemia.

In the partially nephrectomized rat the renal tissue is reduced without directly affecting any other organ, but the degenerative and inflammatory nephropathies of man usually involve not only the kidney but other organs as well. If an analogy can be drawn between the response of man and that of the rat to the loss of urinary protein, it may be assumed that hypoproteinemia in man must be due to interference with the protein-regenerating mechanism. It seems likely that human plasma protein values cannot be elevated with high protein diets and that lowered plasma protein values for human beings with nephrosis must be attributed to altered protein regeneration rather than to proteinuria.

## SUMMARY

The concentrations of plasma protein were determined for large numbers of individual control rats fed diets containing various percentages (10, 20, 40, 60 and 80) of dried extracted beef muscle. The results obtained with the first four diets were almost identical and yielded the following averages: total plasma protein, 6.25 Gm.; albumin, 3.42 Gm.; globulin, 2.83 Gm., and fibrin, 0.28 Gm., per hundred cubic centimeters. The total plasma protein and albumin concentrations for the partially nephrectomized rats were slightly lower, and the fibrin values were slightly higher than these figures, except with diet EB 10,

10. Cutting, W. C., and Cutter, R. D.: Total Plasma Protein in Normal and Fasting Rats, Am. J. Physiol. **113**:150, 1935.

which produced control values. Hypoproteinemia was not encountered in any of these animals.

A comparison of the plasma protein concentrations for partially nephrectomized rats with the amount of protein excreted indicated that there was no decrease of physiologic importance in the total plasma protein and albumin values with increased proteinuria.

It was shown that the partially nephrectomized rat may excrete urinary protein during twenty-four hours in amounts as great as the total circulating plasma protein without evidence of hypoproteinemia.

# EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

## X. BLOOD PLASMA CHOLESTEROL AND PHOSPHOLIPID PHOSPHORUS VALUES FOR CONTROL AND PARTIALLY NEPHRECTOMIZED RATS FED DIETS CONTAINING DRIED EXTRACTED LIVER

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Cholesterol metabolism in renal diseases has been reviewed by Cantarow [1] and by Page and his associates.[2] The probable significance of phospholipids and their relation to free cholesterol have been discussed by Sinclair.[3] It is well known that there is an increased concentration of plasma cholesterol in nephrosis and in the nephrotic types of glomerulonephritis. There appears to be no logical explanation for the changes in the cholesterol values of the blood in these diseases. There has been little work concerning lipid metabolism of experimental animals with renal insufficiency to compare with results obtained for patients with impaired renal function.

It is the purpose of this investigation to study the plasma cholesterol and lipid phosphorus values for partially nephrectomized and control rats fed diets containing varying concentrations of dried extracted liver.

### METHODS

The operative procedure for unilateral and partial nephrectomy, the methods for estimating blood pressure and renal function and the care of the experimental animals have been described.[4] When the animals were 60 to 70 days of age they were placed on one of the experimental diets the composition and cholesterol content of which are listed in table 1. The five diets were designated EL 10,

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This investigation was made possible by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.

1. Cantarow, A.: Cholesterol Metabolism, Internat. Clin. **1**:237, 1935.

2. Page, I. H.; Kirk, E., and Van Slyke, D. D.: Plasma Lipids in Chronic Hemorrhagic Nephritis, J. Clin. Investigation **15**:101, 1936.

3. Sinclair, R.: The Physiology of the Phospholipids, Physiol. Rev. **14**:351, 1934.

4. Chanutin, A., and Ludewig, S.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: V. Diets Containing Whole Dried Meat, Arch. Int. Med. **58**:60 (July) 1936.

EL 20, EL 40, EL 60 and EL 80, in accordance with the percentage of dried extracted liver, which was the principal source of protein. The dried extracted liver was prepared from cold storage hog liver which was thoroughly extracted with hot water and dried.

The minimum period of the experimental diet was sixty days, but in most instances the diet was continued from ninety to one hundred and fifty days before the animal was killed. Blood was drawn from the abdominal aorta while the animal was under ether anesthesia, and heparin was used as the anticoagulant. The method of Schoenheimer and Sperry,[5] with slight modifications,[6] was used for determining the free and total cholesterol values. Phospholipid phosphorus values were determined according to the procedure recommended by Man and Peters.[7] Statistical analyses were done according to standard methods.[8]

## RESULTS

*Plasma Cholesterol Values for Control Animals (One or Two Kidneys) and Partially Nephrectomized Rats.*—The individual values for total cholesterol and the percentage of esterified cholesterol in the

TABLE 1.—*Composition of Rations*

| Diet | Dried Extracted Liver | Starch | Lard | Cod Liver Oil | Dried Yeast | Salt Mixture | Cholesterol, % | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Total | Free | Esters |
| EL 10..... | 10 | 62 | 14 | 5 | 5 | 4 | 0.16 | 0.13 | 23 |
| EL 20..... | 20 | 52 | 14 | 5 | 5 | 4 | 0.29 | 0.19 | 34 |
| EL 40..... | 40 | 32 | 14 | 5 | 5 | 4 | 0.55 | 0.37 | 32 |
| EL 60..... | 60 | 12 | 14 | 5 | 5 | 4 | 0.72 | 0.45 | 37 |
| EL 80..... | 80 | 6 | | 4 | 6 | 4 | 1.07 | 0.63 | 42 |

plasma of control and partially nephrectomized rats fed diets containing 10, 20, 40, 60 or 80 per cent dried extracted liver are presented in figure 1. The mean values for the total cholesterol for the control animals were about the same with the exception of the elevated value with diet EL 80. These average values, in milligrams per hundred cubic centimeters, with standard errors, were $86 \pm 2.32$, $86 \pm 2.89$, $90 \pm 3.72$, $92 \pm 4.02$ and $122 \pm 4.01$, respectively. On the other hand, the mean values for plasma total cholesterol for the partially nephrectomized rats showed an irregular increase with the increased percentage of cholesterol in the respective extracted liver diet. These average

5. Schoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745, 1934.

6. Chanutin, A., and Ludewig, S.: The Blood Plasma Cholesterol and Phospholipid Phosphorus in Rats Following Partial Hepatectomy and Following Ligation of the Bile Duct, J. Biol. Chem. **115**:1, 1936.

7. Man, E. B., and Peters, J. P.: Gravimetric Determination of Serum Cholesterol Adapted to the Man and Gildea Fatty Acid Method, with a Note on the Estimation of Lipoid Phosphorus, J. Biol. Chem. **101**:685, 1933.

8. Garrett, H. E.: Statistics in Psychology and Education, New York, Longmans, Green & Co., 1930.

values, in milligrams per hundred cubic centimeters, with standard errors, were $111 \pm 2.98$, $129 \pm 2.89$, $125 \pm 3.68$, $144 \pm 4.09$ and $150 \pm 5.56$, respectively. These values were higher than those for the control animals in the respective dietary groups. A statistical analysis of the reliability of the difference between the means for the control and those for the partially nephrectomized animals with the same diet showed a significant difference in all cases. For all dietary groups the percentage of esterified cholesterol remained fairly constant, despite the wide variations in the total cholesterol concentrations. Hypoproteinemia was never encountered in these animals.

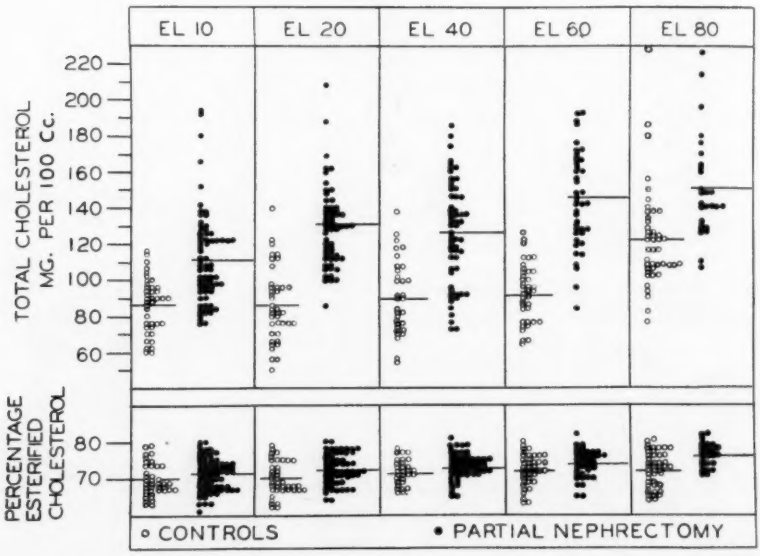


Fig. 1.—Cholesterol values for control and partially nephrectomized rats fed various diets containing dried extracted liver.

It is obvious that renal insufficiency produced by partial nephrectomy affects cholesterol metabolism, as evidenced by the plasma cholesterol concentration. It has been shown [9] that the plasma cholesterol was greater for partially nephrectomized rats than for controls fed a diet supplemented with 2.5 per cent cholesterol. Best, Grant and Ridout [10] have shown that increasing amounts of protein (casein, dried egg white and beef muscle) in the diet prevented the accumulation of fat in the

9. Chanutin, A., and Ludewig, S.: The Effect of Cholesterol Ingestion on Tissue Lipids of Rats, J. Biol. Chem. **102**:57, 1933.

10. Best, C. H.; Grant, R., and Ridout, J. H.: The "Lipotropic" Effect of Dietary Protein, J. Physiol. **86**:337, 1936.

liver of the white rat. This lipotropic effect was difficult to gage in the present experiments because there was a progressive increase in both the protein and the cholesterol content of the diets. It is probable that the slight increase in plasma cholesterol encountered for control animals fed diets containing about 1 per cent cholesterol (diet EL 80) may have been due to the excessive amount of cholesterol in relation to the protein content.

Despite the presence of appreciable amounts of cholesterol in the diets fed in these experiments, gross examination of the livers revealed no fatty changes. Blatherwick and his associates [11] demonstrated that diets rich in whole dried liver caused the development of a fatty liver in the rat. On the other hand, similar quantities of dried, water-extracted liver did not produce these fatty changes. This finding has been confirmed in this investigation.

TABLE 2.—*Ratio of Free Cholesterol to Phospholipid Phosphorus for Control and Partially Nephrectomized Rats* *

| Diet | Control Rats | Partially Nephrectomized Rats |
|---|---|---|
| EL 10 | 3.5 (35) | 3.6 (71) |
| EL 20 | 3.7 (19) | 3.9 (44) |
| EL 40 | 3.7 (15) | 3.6 (59) |
| EL 60 | 3.7 (15) | 3.8 (39) |
| EL 80 | 3.7 (36) | 3.8 (27) |

* The figures in parentheses indicate the number of rats.

*Relation of Free Cholesterol and Phospholipid Values.*—The average $\frac{\text{free cholesterol}}{\text{phospholipid phosphorus}}$ ratios for the control and partially nephrectomized rats are presented in table 2. It is seen that the ratios are constant for both groups of animals. The phospholipid phosphorus concentration varied from 4.3 to 15.3 mg. per hundred cubic centimeters. A similar direct relation was demonstrated in rats subjected to partial hepatectomy and to ligation of the bile duct [6] and in man with hepatic damage.[12]

*Relation Between Total Cholesterol Value, Urea Ratio and Blood Pressure.*—The relation between the total cholesterol value and the urea ratio, $\frac{\text{urine excreted per hour}}{\text{urea in 100 cc. of blood}}$, is presented in figure 2. It can be seen that the concentration of plasma cholesterol was not closely related to the degree of renal insufficiency. In figure 3 the total cholesterol value

11. Blatherwick, N. R.; Medlar, E. M.; Bradshaw, P. J.; Post, A. L., and Sawyer, S. D.: The Dietary Production of Fatty Livers in Rats, J. Biol. Chem. **103**:93, 1933.

12. Chanutin, A., and Ludewig, S.: Blood Lipid Studies in a Case of Xanthomatosis Associated with Hepatic Damage, J. Lab. & Clin. Med. **22**:903, 1937.

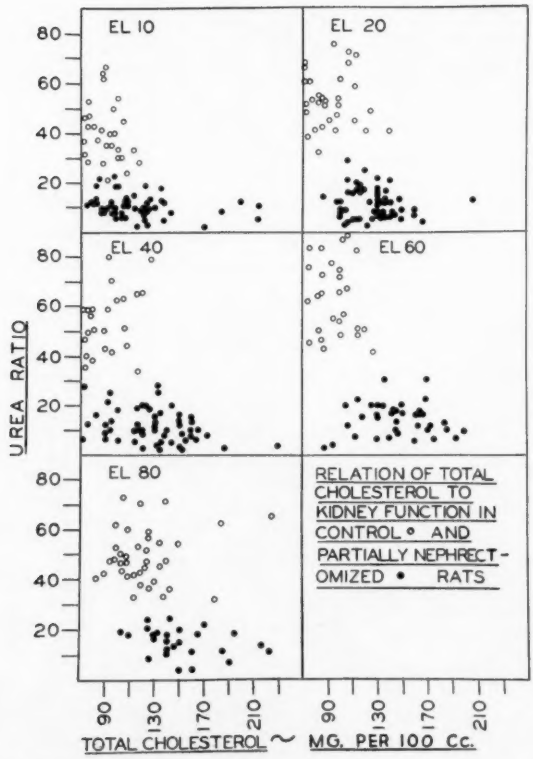


Fig. 2.—Relation of total cholesterol value to renal function of control and partially nephrectomized rats.

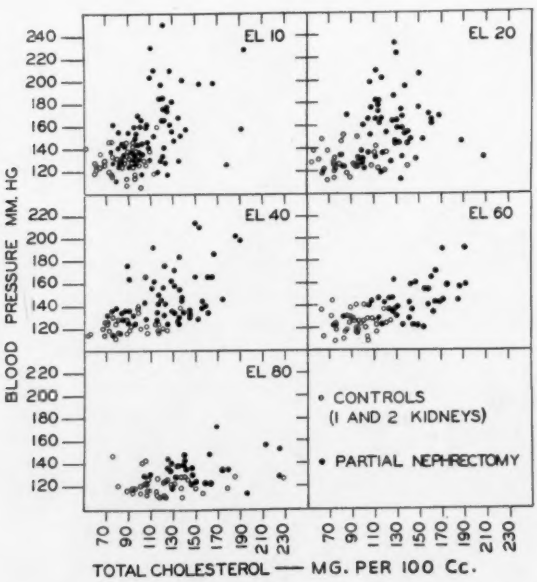


Fig. 3.—Comparison of the total cholesterol values and the blood pressure.

is compared with the blood pressure. There was no definite relation between the height of the blood pressure and the plasma cholesterol concentration.

## SUMMARY AND CONCLUSIONS

The plasma cholesterol and phospholipid phosphorus concentrations have been determined for control (one or two kidneys) and partially nephrectomized rats fed diets containing varying percentages of dried extracted liver (10, 20, 40, 60 and 80 per cent) and cholesterol (0.16 to 1.07 per cent).

There was no increase in the mean concentration of the plasma cholesterol for control animals except for those receiving diet EL 80. There was an increase in the cholesterol values for the partially nephrectomized rats which appeared to be roughly associated with the amount of ingested cholesterol. There was no relation between the total plasma cholesterol concentration and the renal function or the blood pressure. The phospholipid phosphorus value varied directly with the free cholesterol concentration for both the control and the partially nephrectomized animals. The percentage of cholesterol esters was unchanged by operation or by diet.

Since renal insufficiency produced by partial nephrectomy appears to affect the ability of the rat to metabolize cholesterol, it is likely that cholesterol disturbances in renal diseases of man are directly associated with renal damage.

# SIZE AND SHAPE OF THE HEART IN HYPERTHYROIDISM

## A TELEROENTGENOGRAPHIC STUDY OF TWO HUNDRED CASES

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Until recently "thyroid heart" was considered to be a definite entity and was admitted without discussion as a member of the group of organic cardiac diseases. This idea is now losing popularity, and the tendency to consider so-called thyroid heart as a simple functional disorder is becoming more and more prevalent.

The fundamental reasons for this change are based on experimental proof—pathologico-anatomic, electrocardiographic and roentgenographic, though none of these has been capable of showing definitely the existence of a constant specific alteration in the heart in hyperthyroidism. Thus, Takane [1] and Boyksen [2] have found infiltration or degenerative changes in the hearts of rats intoxicated with thyroid preparations, whereas Goodpasture [3] found only slight alterations in rabbits under similar conditions, but he admitted that there might exist an increased liability of the myocardium to infection. Rake and McEachern [4] said they considered that the lesions they observed were of no importance. Simonds and Brandes,[5] working with dogs, mentioned only hypertrophy.

Postmortem examination of the human subject also has given rise to divergent interpretations. Fahr and Kuhle [6] observed hypertrophy,

From the Department of Surgery, the Rawson Hospital, Prof. E. Finochietto, director.

1. Takane, K.: Pathobiogenese der Myocarditis acuta durch organische und anorganische Jodbindungen bzw. der Basedowmyokarditis, Virchows Arch. f. path. Anat. **259**:1, 1926; Ueber die experimentelle akute Myokarditis durch Thyreoidin und Jodsalze, ibid. **259**:737, 1926.

2. Boyksen, D.: Thyreotoxische Herzmuskelschädigungen, Virchows Arch. f. path. Anat. **293**:342, 1934.

3. Goodpasture, E.: The Influence of Thyroid Products on the Production of Myocardial Necrosis, J. Exper. Med. **34**:407, 1921.

4. Rake, G., and McEachern, D.: Experimental Hyperthyroidism and Its Effects upon the Myocardium in Guinea Pigs and Rabbits, J. Exper. Med. **54**:23, 1934.

5. Simonds, J. P., and Brandes, W. W.: The Size of the Heart in Experimental Hyperthyroidism, Arch. Int. Med. **45**:503 (April) 1930.

6. Fahr, T., and Kuhle, J.: Zur Frage des Kropfherzens und der Herzveränderungen bei Status thymolymphaticus, Virchows Arch. f. path. Anat. **233**: 286, 1921.

myodegeneration, callus formation and lymphocytic infiltration and said they concluded that myocarditis could be attributed to the thyroid disease, although they recognized the nonspecific character of the lesion. Boyksen [2] made similar observations and also described necrotic alterations. Baust [7] mentioned only a slight increase of lymphocytes, histiocytes and fibroblasts. De Chatel and Molnár [8] observed dark brown pigmentation, an increase of connective tissue and slight hypertrophy. On the other hand, Cabot; [9] Rake and McEachern; [10] Lewis; [11] Weller, Wanstrom, Gordon and Bugher,[12] and Friedberg and Sohval [13] did not note much change, and when they did they attributed it to concomitant lesions due to rheumatism, arteriosclerosis, syphilis or some other disease. References to publications based on the observations made at only a small number of autopsies have been omitted.

In electrocardiographic studies there is agreement in the frequency with which auricular fibrillation occurs, but there the unanimity ends. Hoffmann,[14] Strubell,[15] Krumbhaar,[16] Haas and Parade,[17] Gossels,[18] and McGuire and Foulger [19] have said they consider that a high T wave is characteristic of hyperthyroidism, but Smith and Colvin,[20]

7. Baust, H.: Ueber histologische Befunde an Kropfherzen, Beitr. z. path. Anat. u. z. allg. Path. **86**:543, 1931.

8. de Chatel, A., and Molnár, W.: Herzveränderungen bei Morbus Basedow, Virchows Arch. f. path. Anat. **289**:557, 1933.

9. Cabot, R.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, p. 723.

10. Rake, G., and McEachern, D.: A Study of the Heart in Hyperthyroidism, Am. Heart J. **8**:19, 1932.

11. Lewis, W.: Hyperthyroidism and Associated Pathology, Am. J. M. Sc. **171**:65, 1931.

12. Weller, C. V.; Wanstrom, R. C.; Gordon, H., and Bugher, J. C.: Cardiac Histopathology in Thyroid Disease, Am. Heart J. **8**:8, 1932.

13. Friedberg, C., and Sohval, A.: The Occurrence and the Pathogenesis of Cardiac Hypertrophy in Graves' Disease, Am. Heart J. **13**:599, 1937.

14. Hoffmann, A.: Die Elektrographie als Untersuchungsmethode des Herzens und ihre Ergebnisse, Munich, J. F. Bergmann, 1914, p. 115.

15. Strubell, A.: Ueber die Klinik des Elektrokardiogramms, Deutsche med. Wchnschr. **38**:988, 1912.

16. Krumbhaar, E.: Electrocardiographic Observations in Toxic Goiter, Am. J. M. Sc. **155**:175, 1928.

17. Haas, M., and Parade, G.: Untersuchungen bei Morbus Basedow vor und nach Schilddrüsenresektion, Beitr. z. klin. Chir. **152**:111, 1931.

18. Gossels, C.: Klinischer Beitrag zur Frage des Elektrokardiogramms bei Schilddrüsenveränderungen, Deutsches Arch. f. klin. Med. **173**:597, 1932.

19. McGuire, J., and Foulger, M.: The Influence of Thyroid Extract and Hyperthyroidism on the Electrocardiogram with Special Reference to the T-Waves, Am. Heart J. **8**:114, 1932.

20. Smith, F., and Colvin, L.: Certain Cardio-Vascular Features of Hyperthyroidism, Ann. Clin. Med. **5**:616, 1927.

Franke,[21] White,[22] Misske and Schöne [23] and Gotta [24] have not expressed agreement with this.

Roentgenographic studies have revealed the so-called thyroid heart in two of its aspects—shape and size. Otten,[25] Kerr and Hensel,[26] Rösler,[27] Meyer-Borstel,[28] Parkinson and Cookson,[29] Cookson [30] and Peserico [31] have admitted that hyperthyroidism causes a bulging of the left middle arch, which makes the cardiac shadow show the so-called mitral configuration; according to some authors,[32] when the hyperthyroidism is prolonged, the cardiac area is enlarged chiefly on the left side. On the other hand, Hawley [33] has maintained that the so-called thyroid heart has no characteristic shape, and Misske and Schöne [34] have attributed the mitral configuration in cases of hyperthyroidism to purely constitutional factors. Hamilton,[35] Smith and Colvin,[36] Deneen [36] and Hurxthal and Menard [37] have stated that the heart in hyperthyroidism is of normal size or only slightly enlarged and that in

21. Franke, W.: Das Elektrocardiogram bei Schilddrüsenerkrankungen, Deutsches Arch. f. klin. Med. **159**:180, 1928.

22. White, P. D.: Heart Disease, New York, The Macmillan Company, 1935, p. 379.

23. Misske, B., and Schöne, G.: Das Elektrokardiogramm bei Schilddrüsenüberfunktion, Ztschr. f. klin. Med. **125**:387, 1933.

24. Gotta, H.: Contribucion al estudio de la tirotoxicosis, Buenos Aires, Frascoli y Bindi, 1931, p. 44.

25. Otten, M.: Die Bedeutung der Orthodiagraphie für die Erkennung der beginnenden Herzerweiterung, Deutsches Arch. f. klin. Med. **105**:370, 1910.

26. Kerr, W. J., and Hensel, G. C.: Observations of the Cardiovascular System in Thyroid Disease, California State J. Med. **20**:306, 1922; Arch. Int. Med. **31**:398 (March) 1923.

27. Rösler, H.: Das Röntgenbild des Herzens beim hyperthyroidismus, Wien. Arch. f. inn. Med. **15**:539, 1928.

28. Meyer-Borstel, H.: Ueber Form- und Grössenveränderungen des Herzens bei Struma, Fortschr. a. d. Geb. d. Röntgenstrahlen **41**:695, 1930.

29. Parkinson, J., and Cookson, H.: The Size and Shape of the Heart in Goiter, Quart. J. Med. **24**:499, 1931.

30. Cookson, H.: The Size and Shape of the Heart in Goiter, Proc. Roy. Soc. Med. **25**:1517, 1932.

31. Peserico, E.: Le cardiopatie nell'ipertiroidismo, cuore e circolaz. **18**:83, 1934.

32. Kerr and Hensel.[26] Parkinson and Cookson.[29] Cookson.[30]

33. Hawley, S.: A Roentgen Study of the Chest in Two Hundred Patients with Goiter, Am. J. Roentgenol. **32**:326, 1934.

34. Misske, B., and Schöne, G.: Das Herz im Röntgenbilde bei Schilddrüsenüberfunktion, Fortschr. a. d. Geb. d. Röntgenstrahlen **50**:121, 1935.

35. Hamilton, B.: Heart Failure of the Congestive Type Caused by Hyperthyroidism, J. A. M. A. **83**:405 (Aug. 9) 1924.

36. Deneen, F.: The Heart in Goiter Conditions, Illinois M. J. **55**:264, 1929.

37. Hurxthal, L., and Menard, O.: The Size of the Heart in Goiter: A Teleradiographic Study, Am. J. M. Sc. **180**:772, 1930.

the cases in which there is enlargement of the cardiac area there is other cardiovascular disease present, notably rheumatism, hypertension, arteriosclerosis or syphilis.

This contradictory state of opinion has led to the publication of this work, based on the clinical, electrocardiographic and teleroentgenographic study of a series of 200 cases of hyperthyroidism. The teleroentgenographic study was repeated after various intervals in 86 cases; in 12 cases the hyperthyroidism persisted, and in 74 cases recovery had been achieved.

The clinical examination was performed by me in every case, and the diagnosis was confirmed by means of repeated basal metabolic estimations. The teleroentgenograms were made with the patient upright, with frontal projection at a focal distance of 2 meters, with an exposure of one-tenth second and during normal inspiration.

The internal diameter of the chest and the transverse and long diameters of the heart were measured on each roentgenogram, and the changes in shape and size were noted. The size of the cardiac area was classified as normal, slightly enlarged, appreciably enlarged or greatly enlarged. The classification was made according to personal judgment, which is naturally open to criticism, but in spite of the imperfections of such a method, it seemed preferable to the use of the cardiothoracic index or tables of standard values, which do not take into account individual constitutional variations. On the other hand, the expressions normal, appreciably enlarged and greatly enlarged correspond to a definite concept that is easy to interpret. This is not so, however, when the term slightly enlarged is used. In this category were placed the cases in which enlargement was doubtful, and it included a borderline or transitional appearance between normal and undoubted enlargement.

With this classification it was found that the cardiac area was normal in 80 cases of hyperthyroidism, slightly enlarged in 64, appreciably enlarged in 30 and greatly enlarged in 26.

Next it was decided to investigate whether this discrepant variation was due to the influence of any of the following factors: (1) the age of the patient, (2) the duration of hyperthyroidism, (3) the intensity of hyperthyroidism or (4) associated cardiovascular disease.

1. In order to investigate a possible relation between the size of the cardiac area and the age of the patient, the patients were divided into three groups according to age: in the first, those under 29; in the second, those from 30 to 49, and in the third, those over 50.

Table 1 shows the results of this classification. In each column under the number of patients is given the percentage in relation to the total of patients in the group. The total number of patients in each group, was as follows: 93 in the first, 83 in the second and 24 in the third.

Comparing the percentages it can be seen that of those under 29 years, half showed a normal cardiac area, one-third showed slight enlargement and a small number showed great enlargement. For those

between 30 and 49 years of age, these differences lessened and for those over 50 the proportions changed, only one-sixth showing a normal cardiac area and more than one-third showing great enlargement. Thus, with these statistical data it can be asserted that the number of patients with hyperthyroidism who show enlargement of the cardiac area increases with age.

2. In order to investigate the possibility of a relation between the size of the heart and the duration of hyperthyroidism, the patients were divided into three groups according to whether the disease had existed (1) for less than one year, (2) for from one to five years or (3) for more than five years.

TABLE 1.—*Relation of Age to the Cardiac Area*

| Age Group | Number of Patients | Cardiac Area | | | |
|---|---|---|---|---|---|
| | | N | + | ++ | +++ |
| Less than 29 years | 93 | 44<br>47% | 32<br>34% | 13<br>14% | 4<br>4% |
| Between 30 and 49 years | 83 | 32<br>38% | 26<br>31% | 12<br>14% | 13<br>15% |
| Over 50 | 24 | 4<br>16% | 6<br>25% | 5<br>20% | 9<br>37% |

* In tables 1 to 6, N indicates normal; +, slight enlargement; ++, appreciable enlargement; +++, great enlargement.

TABLE 2.—*Relation of the Duration of Hyperthyroidism to the Cardiac Area*

| Duration of Hyperthyroidism | Number of Patients | Cardiac Area | | | |
|---|---|---|---|---|---|
| | | N | + | ++ | +++ |
| Less than 1 year | 70 | 33<br>47% | 22<br>31% | 11<br>15% | 4<br>6% |
| 1 to 5 years | 82 | 32<br>39% | 27<br>32% | 7<br>8% | 16<br>19% |
| More than 5 years | 42 | 14<br>33% | 14<br>33% | 9<br>21% | 5<br>11% |

Table 2 shows the result of this classification. Each column gives the number of cases and the corresponding percentage in relation to the total number of patients. The total numbers were 70, 82 and 42, respectively, for the three groups; 6 patients were not included, as the time of beginning of the disease in these cases could not be established.

Comparison of the percentages revealed that as the disease continued, the relative number of patients with a normal cardiac area diminished and the number of patients with cardiac enlargement increased, but this increase was not regular nor very significant, as can be seen by comparing the figures in the last two columns.

Considering the table as a whole, one may assume that there is a relation, though indeed not pronounced, between the cardiac area and the duration of the hyperthyroidism.

3. To examine the possibility of a relation between the cardiac area and the degree of hyperthyroidism, the patients were divided into the three following groups according to the basal metabolic rate: under + 35 per cent, between + 35 per cent and + 50 per cent and above + 50 per cent.

In accordance with the system adopted for the preceding tables, in table 3 each column contains the number of patients and the corresponding percentage in relation to the total number of patients in the group. The totals were 38, 67 and 95, respectively, for the three groups.

Examination of the percentages shows that among patients with moderate hyperthyroidism, the proportion of normal cardiac areas was relatively greater than for those with more intense hyperthyroidism. These statistical data suggest the existence of a relation between the intensity of hyperthyroidism and the cardiac area, but it is not sufficiently decisive to be stated definitely.

TABLE 3.—*Relation of the Basal Metabolic Rate and the Cardiac Area*

| Basal Metabolic Rate | Number of Patients | Cardiac Area | | | |
|---|---|---|---|---|---|
| | | N | + | ++ | +++ |
| Under +35% | 38 | 21<br>55% | 13<br>34% | 2<br>5% | 2<br>5% |
| +35 to +50% | 67 | 33<br>49% | 18<br>26% | 10<br>14% | 6<br>9% |
| Above +50% | 95 | 26<br>27% | 33<br>34% | 18<br>18% | 18<br>18% |

4. The existence of diseases recognized as capable of producing enlargement of the cardiac area, particularly arteriosclerotic disease, hypertension, rheumatism and renal disease with hypertension, was carefully investigated in each case of hyperthyroidism both from the clinical and from the roentgenographic point of view. The diagnosis was carefully made and was based on undoubted symptoms. Some patients had symptoms which indicated that cardiovascular lesions might be presumed to be present, but this point could not be definitely affirmed or denied; in these instances the symptoms were considered as nonexistent.

A diagnosis of arterial hypertension was made only for those patients in whom this condition persisted after they had recovered from hyperthyroidism, thus covering the objections of those who maintain that hyperthyroidism per se can cause hypertension (Parkinson and Hoyle[38]); in only 2 cases of hyperthyroidism, in which the patients have been followed for eight and seven years, respectively, and in which cure has

38. Parkinson, J., and Hoyle, C.: Thyrotoxic Hypertension, Lancet **2**:913, 1934.

not yet been obtained, was this condition not fulfilled, but the high blood pressure in these cases makes the diagnosis certain.

A diagnosis of rheumatism was made only for those patients who had an absolutely characteristic history of rheumatic fever or chorea or of aortic regurgitation not due to other known causes or when the existence of mitral stenosis was confirmed after recovery from hyperthyroidism. In this way mistakes due to the frequency and variety of murmurs which occur during hyperthyroidism were avoided. The case of a woman who had a greatly enlarged heart was also included, although the rheumatic origin could not be proved; this patient was not followed afterward, but she died later from an attack of tetany, and pericardial effusion was present at autopsy.

Sclerotic disease of the aorta was noted in 23 cases, arterial hypertension in 14, a history of or actual rheumatic lesions in 19 and glomerular nephritis in 4.

TABLE 4.—*Relation of Associated Diseases to Cardiac Area*

| Associated Disease | Number of Patients | Cardiac Area | | | |
|---|---|---|---|---|---|
| | | N | + | ++ | +++ |
| Sclerotic aortic disease | 23 | 3 | 5 | 8 | 7 |
| Hypertension | 14 | .. | 5 | 2 | 7 |
| Rheumatism | 19 | 2 | 3 | 9 | 5 |
| Glomerular nephritis | 4 | .. | 1 | 1 | 2 |
| Totals | 60 | 5 | 14 | 20 | 21 |

In table 4 the patients suffering from these diseases are grouped according to the size of the heart.

Comparing the total number of patients in the corresponding groups in which some other disease was present as well as hyperthyroidism, it is seen that 21 (80 per cent) of the 26 patients with great enlargement of the heart had some associated disease which was admittedly capable of producing cardiac enlargement. Twenty (66 per cent) of the 30 patients who had an appreciable enlargement of the heart had also one of the four previously mentioned diseases. The percentages were reduced to 21 and 6 per cent, respectively, for those with a moderately enlarged or normal heart.

It can therefore be concluded that the greater number of patients with hyperthyroidism and enlargement of the heart have some other disease which would account for this enlargement.

5. Twelve patients were studied roentgenographically on two separate occasions during the disease, the second roentgenogram being taken when the hyperthyroidism was still present or even—and this must be emphasized—of greater intensity than at the previous examination. In table 5 each case is individually analyzed.

TABLE 5.—*Summary of Data Obtained from Two Teleroentgenographic Studies During Hyperthyroidism*

| Patient No. | Age, Yr. | Duration of Disease, Yr. | Teleroentgenograms: First: Cardiac Diameters, Cm.: Long | First: Cardiac Diameters, Cm.: Transverse | First: Internal Diameter of Chest, Cm. | First: Cardiac Area | Second: Cardiac Diameters, Cm.: Long | Second: Cardiac Diameters, Cm.: Transverse | Second: Internal Diameter of Chest, Cm. | Second: Cardiac Area | Interval Between Two Roentgenograms: Yr. | Interval Between Two Roentgenograms: Mo. | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 35 | 14 | 15.5 | 13.7 | 30.0 | N | 14.5 | 13.4 | 32.4 | N | 7 | .. | Diaphragm was lower in second plate, thus accounting for apparently reduced area |
| 2 | 27 | 14 | 13.0 | 11.4 | 23.3 | N | 13.0 | 12.0 | 24.2 | N | 2 | .. | |
| 3 | 42 | 1 | 13.1 | 11.1 | 26.5 | N | 13.4 | 11.6 | 24.0 | N | .. | 1 | Diaphragm was raised in second plate, thus accounting for apparently increased area |
| 4 | 6 | 1 | 8.1 | 7.5 | 17.0 | N | 13.1 | 11.5 | 20.3 | +++ | 1 | 10 | Progressive rheumatic heart disease |
| 5 | 44 | 1 | 15.0 | 14.2 | 24.3 | + | 15.0 | 14.0 | 26.0 | + | 1 | 10 | Arterial hypertension |
| 6 | 52 | 17 | 15.2 | 14.3 | 25.0 | + | 15.4 | 14.0 | 27.4 | + | 1 | 3 | Sclerotic aortic disease |
| 7 | 56 | 22 | 14.6 | 12.8 | 28.0 | ++ | 14.2 | 13.0 | 27.2 | ++ | 3 | 3 | Sclerotic aortic disease |
| 8 | 29 | 4 | 14.3 | 13.1 | 24.0 | ++ | 14.0 | 13.3 | 24.0 | ++ | .. | 6 | Rheumatic endocarditis |
| 9 | 25 | 18 | 13.1 | 13.2 | 23.5 | ++ | 14.6 | 14.1 | 24.5 | ++ | 5 | 8 | Arterial hypertension; maximum 15 mm., minimum 7 mm. in 1929; maximum 19 mm., minimum 9 mm. in 1935 |
| 10 | 38 | 10 | 14.3 | 13.0 | 23.0 | ++ | 13.8 | 13.8 | 24.2 | ++ | 6 | 6 | Arterial hypertension; maximum 14 mm., minimum 8 mm. in 1930; maximum 19 mm., minimum 11 mm. in 1937 |
| 11 | 38 | 4 | 15.0 | 14.7 | 24.0 | ++ | 16.0 | 14.2 | ? | ++ | 2 | .. | Auricular fibrillation; congestive heart failure |
| 12 | 24 | 1 | 14.8 | 13.8 | 25.6 | ++ | 17.7 | 17.3 | 27.5 | ++++ | 1 | 8 | Glomerulonephritis |

In 7 cases (1 to 3 and 5 to 8) there was no increase in the cardiac area during the two years and three months, which was the average time which elapsed between the taking of the two roentgenograms. Case 1 is worthy of special mention since the second roentgenogram was not taken until seven years after the first, when the hyperthyroidism was clearly worse.

In 3 cases there was a moderate increase in the size of the heart. In cases 9 and 10 this coincided with the increase in arterial hypertension which was associated with the hyperthyroidism, while in case 11 the enlargement was not significant, as the patient also suffered from auricular fibrillation and congestive heart failure.

There remain for consideration cases 4 and 12, in which there was considerable increase in the size of the heart after a relatively short interval; in the first case this was due to rheumatic carditis and in the second to rapidly progressive glomerular nephritis.

Thus, in none of these cases did hyperthyroidism by itself seem capable of producing cardiac enlargement. In every case in which cardiac enlargement did occur, it could be satisfactorily explained as due to some other disease that was present at the same time.

6. Seventy-four patients were studied roentgenographically a second time after they had been submitted to subtotal thyroidectomy; 27 showed a normal cardiac area; 31, slight enlargement; 7, appreciable enlargement, and 9, great enlargement. The clinical examination and basal metabolic results showed that the hyperthyroidism had been cured. The interval between operation and the taking of the roentgenogram varied greatly, owing to individual circumstances; in some cases, when the patient had to return to the province, the interval was scarcely a month, but usually it was more than a year, and in some cases it even reached six or seven years.

On comparison of these roentgenograms and those obtained while the patients were under the influence of hyperthyroidism, three types of conditions were noted: The cardiac area was larger, equal or smaller. The cardiac area was considered as not having changed when the difference in measurements of the long and of the transverse diameter of the heart in the two roentgenograms was less than 0.5 cm. It is extremely difficult to take two roentgenograms under exactly similar conditions, since the heart may not be in the same period of contraction and the patient may hold his breath at a different movement of respiration; hence, a slight difference in measurement must be overlooked.

By using this criterion it was found that after recovery from hyperthyroidism there was no change in the cardiac area in 38 cases, i e.,

more than half the cases (18 patients had a normal cardiac area; 15, slight enlargement; 4, appreciable enlargement, and 1, great enlargement).

The cardiac area was larger in the second roentgenogram in 23 cases (8 patients showed a normal area; 10, slight enlargement; 2, appreciable enlargement, and 3, great enlargement). In some cases there may have been only apparent enlargement, owing to the causes previously mentioned, but in others it might have been a true enlargement, resulting from the cessation of tachycardia, from the progress of preexisting lesions unrelated to hyperthyroidism or from some new disease. Whatever the reason may have been, no useful knowledge is added to the problem of the so-called thyroid heart because, obviously, this enlargement of the cardiac area cannot be a result of the recovery from hyperthyroidism.

The cardiac area was smaller in the second roentgenogram in 13 cases. In 3 cases the decrease was probably only apparent, since the diaphragm was lower than in the original roentgenogram and it is known that when inspiration is deeper the frontal projection of the heart is reduced.

Excluding these, there remain 10 patients (4 with slight enlargement of the cardiac area, 1 with appreciable enlargement and 5 with great enlargement) who almost certainly showed a real decrease in the cardiac volume, although the cardiac area remained larger in comparison with the normal heart. Of these patients, 1 had coronary disease, 1 had arteriosclerotic aortic disease and congestive heart failure, 1 had active rheumatism, 1 had a history of rheumatic fever and congestive heart failure, 4 had permanent auricular fibrillation (3 of these also had arterial hypertension and the fourth patient had congestive heart failure). In the 4 with auricular fibrillation the sinus cardiac rhythm had been established when the second roentgenogram was taken, and all with congestive heart failure had recovered or improved.

It appears, therefore, that the patients in whom the heart became smaller on recovery from hyperthyroidism almost always showed some associated cardiovascular disease, which also explains why, in spite of this decrease in size, the heart remained larger than normal, as has already been stated.

Thus, in more than half the patients studied, recovery from hyperthyroidism was not accompanied with modification of the cardiac area; in about one third of the patients for whom an increase in the cardiac area was found, this could not logically be attributed to the hyperthyroidism; the decrease in the cardiac area found in less than one seventh of the patients almost always occurred in cases of hyperthyroidism associated with cardiovascular disease. Meyer-Borstel.[28]

Menard and Hurxthal,[39] Rosenblum and Levine[40] and Parade and Rahm,[41] who have also made comparative studies of the cardiac area before and after recovery from hyperthyroidism, arrived at a similar conclusion.

## COMMENT

An attempt will now be made to rationalize the conclusions which were reached.

According to the tables, it has been seen that there exists a relation between the cardiac area and certain other factors, none of which have such a distinct influence as the coexistence of cardiovascular disease. This is so evident that it suggests the possibility that the undoubted influence of age and, in a lesser degree, the influence due to the duration and intensity of the hyperthyroidism have an effect only when heart disease is also present. In order to justify this assertion the previously mentioned factors will be reconsidered in the same order.

*Age.*—The number of patients over 30 years of age with an appreciably or greatly enlarged heart was 39; of these, 31 had associated cardiovascular disease. These figures need no comment, and it can be affirmed that although the proportion of hyperthyroidism in patients with enlargement of the heart increases with age, the latter is not the determining factor. This finding is merely due to the fact that the percentage of persons with cardiovascular disease also increases with age.

*Duration of Hyperthyroidism.*—The statistical data concerning the influence of the duration of hyperthyroidism on the heart were not conclusive. There was a slight relation between these two factors, but it is necessary to examine this point further.

It will be remembered that for 7 patients who were studied roentgenographically twice, with an average of two and one-fourth years' time between the two examinations, there was no difference in the cardiac area.

The number of patients suffering from hyperthyroidism of more than one year's standing who showed an appreciably or greatly enlarged cardiac area was 37 (table 2), and 27 of these had associated cardiovascular disease.

These observations enable one to deduce that the duration of hyperthyroidism itself is not the responsible factor in the enlarging of the

39. Menard, O., and Hurxthal, L.: Changes Observed in the Heart Shadow in Toxic Goiter Before and After Treatment, Ann. Int. Med. **6**:1634, 1933.

40. Rosenblum, H., and Levine, S.: What Happens Eventually to Patients with Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy? Am. J. M. Sc. **185**:219, 1933.

41. Parade, G. W., and Rahm, H.: Ueber das Verhalten der Herzgrösse bei Morbus Basedow nach Schilddrüsenresektion, Ztschr. f. klin. Med. **126**:667, 1934.

cardiac area. Hurxthal and Menard,[37] Read [42] and Lerman and Means [43] have stated that they agree with this, but it is not in accordance with the postmortem observations of Kepler and Barnes,[44] who found that there was a relation between the increase in weight of the heart, i. e., hypertrophy, and the duration of hyperthyroidism.

*Intensity of Hyperthyroidism.*—The statistical data, as such, do not permit the assertion that the intensity of hyperthyroidism is a definite factor in the increase in the cardiac area, but these figures become more significant when it is realized that 28 of the 36 patients with a basal metabolic rate above + 50 per cent and an appreciably or greatly enlarged cardiac area (table 3) had associated cardiovascular disease.

It can therefore be affirmed that the intensity of hyperthyroidism is not a factor which causes variations in the size of the heart. Kepler and Barnes,[44] in mentioning the results of many autopsies, said that they had observed no relation between the weight of the heart and the intensity of the hyperthyroidism.

A further confirmation of this assertion is found in the group of patients with thyrocardiac disease (Lahey) who frequently show only a moderate increase in the basal metabolic rate but marked cardiopathic symptoms, particularly enlargement of the heart.

Besides, during a crisis of hyperthyroidism, i. e., in maximum hyperthyroidism, cardiac failure, according to Willius and Boothby,[45] Hamilton [46] and Andrus,[47] does not usually occur, as I also have seen in such cases. Moreover, autopsies on patients with hyperthyroidism who die during the crisis do not reveal enlargement of the heart (Cabot [9]).

The decrease in cardiac area after recovery from hyperthyroidism observed in some cases can be explained in the following way: Hyperthyroidism imposes extra work, which must be performed by a heart already weakened by cardiovascular disease, which was present in almost all the patients examined; when hyperthyroidism was cured, the conditions under which the heart worked were improved, and the size of the heart therefore decreased.

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42. Read, M.: Cardiac Status After Prolonged Thyrotoxicosis, Am. Heart J. **8**:84, 1932.

43. Lerman, J., and Means, J.: Cardiovascular Symptomatology in Exophthalmic Goiter, Am. Heart J. **8**:55, 1932.

44. Kepler, E., and Barnes, A.: Congestive Heart Failure and Hypertrophy in Hyperthyroidism, Am. Heart J. **8**:102, 1932.

45. Willius, F., and Boothby, W.: The Heart in Exophthalmic Goiter and Adenoma with Hyperthyroidism, M. Clin. North America **7**:189, 1923.

46. Hamilton, B.: Clinical Notes on Hearts in Hyperthyroidism, Boston M. & S. J. **186**:216, 1922.

47. Andrus, E.: The Heart in Hyperthyroidism: A Clinical and Experimental Study, Am. Heart J. **8**:66, 1932.

It can be concluded that age and the duration and intensity of the hyperthyroidism are not determining factors in the enlargement of the cardiac area which is found in some patients with hyperthyroidism.

*Mitral Configuration.*—It has been said by certain authors [48] that the cardiac shadow in cases of hyperthyroidism often shows mitral configuration. The frequency of the bulging of the left middle arch was examined; only 4 of the 67 patients in whom it was found had mitral stenosis. The age of the patient, the intensity and duration of hyperthyroidism and the size of the heart had no influence on the production of this shape (statistical data are suppressed); hence, it can be looked on as of constitutional origin (Borak,[49] Német [50] and Misske and Schöne [34]) and not as mitral configuration due to hyperthyroidism. This interpretation is also supported by the fact that in 26 patients with so-called mitral configuration, the latter persisted when roentgenograms were made after recovery from the hyperthyroidism, there being a decrease in the curvature of the left arch in only a few cases.

TABLE 6.—*Relation of Electrocardiographic Findings to Cardiac Area*

| Electrocardiographic Findings | Number of Patients | Cardiac Area | | | |
|---|---|---|---|---|---|
| | | N | + | ++ | +++ |
| Normal | 108 | 55 | 37 | 11 | 5 |
| Auricular fibrillation | 13 | 1 | 2 | 5 | 5 |
| Auricular fibrillation and left axis deviation | 7 | .. | 1 | 1 | 5 |
| Left axis deviation | 39 | 11 | 10 | 9 | 9 |
| Disturbances of conduction | 3 | 1 | 2 | .. | .. |

*Electrocardiography.*—The analysis of the electrocardiograms obtained for patients suffering from hyperthyroidism does not come within the scope of this paper, but it is interesting to examine briefly the electrocardiographic records of the patients for whom roentgenograms were also made.

In 170 cases an electrocardiogram was taken; in 108 the tracing was normal and usually showed only sinus tachycardia; in 20 cases there was auricular fibrillation, accompanied in 7 cases with deviation of the electrical axis to the left. In 35 cases there was only deviation to the left of the electrical axis, with ventricular extrasystoles in 4 cases and finally in 3 cases, disturbances in the intraventricular conduction.

In table 6 the patients for whom electrocardiograms were made are grouped according to the size of the heart. It can be seen that there

48. Otten.[25] Kerr and Hensel.[26] Rösler.[27] Meyer-Borstel.[28] Parkinson and Cookson.[29] Cookson.[30] Peserico.[31]

49. Borak, J.: Fortschr. a. d. Geb. d. Röntgenstrahlen **32**:137, 1924.

50. Német, G.: Zur Kenntnis der "Mitralform" gesunder Herzen, Klin. Wchnschr. **2**:348, 1923.

were relatively few patients with a normal electrocardiogram among those with an appreciably or greatly enlarged cardiac area, and these usually showed auricular fibrillation or deviation to the left of the electrical axis. This is a natural finding, since, as has been shown, the majority of the patients with hyperthyroidism in these groups have antecedents of rheumatic fever or also suffer from arterial hypertension or degenerative aortic lesions.

In 64 cases another electrocardiogram was made when the hyperthyroidism had been cured, and it was found that the tachycardia in almost all cases had disappeared. In 9 cases in which there had previously been fibrillation, the sinus rhythm was reestablished, but in the rest of the cases the records did not show any substantial change. In those cases in which there was some disturbance of the intraventricular conduction, the electrocardiogram was not modified.

Thus, there is therefore a suggestive parallel between the electrocardiographic and roentgenographic findings, as both demonstrate the absence of an organic lesion which can be ascribed to hyperthyroidism, since in the cases in which there is modification, usually some other cardiovascular disease is present which can account for it.

SUMMARY

Hyperthyroidism brings about slight or no increase of the cardiac area.

When the cardiac area is increased in a patient suffering from hyperthyroidism, this is due to some cardiovascular disease that is also present.

Recovery from hyperthyroidism is only in a minor number of cases accompanied with reduction of the cardiac area, which to a certain extent is a confirmation of the first two conclusions.

Certain objections may be brought forward and must be discussed:

1. This work is based on the results of teleroentgenograms taken in frontal projection, thus measuring the size of the heart in one plane only. If, however, hyperthyroidism causes some change in the volume of the heart, it is reasonable to think this would be complete and therefore apparent in any plane examined. The possibility that bulging of the left middle arch is due to partial and incipient dilatation has been discarded.

2. Teleroentgenography does not offer an accurate method of measuring the cardiac area, since changes of less than 10 per cent are not registered. Because of this, the possibility that the cardiac area may be somewhat enlarged in cases of hyperthyroidism has not been denied

3. Stewart and Hamilton [51] have asserted that tachycardia causes a decrease in the size of the heart; in which case, since the majority of patients with hyperthyroidism suffer from tachycardia, this would hide the real increase in volume. These authors, however, have only mentioned patients with tachycardia of short duration, and it is unlikely that this conclusion can also be applied in cases of long-standing tachycardia.

4. The patients with moderate cardiac enlargement have not been sufficiently taken into account in formulating the foregoing conclusions. Since in only a fourth of these patients could some other cardiovascular disease be demonstrated, it might be supposed that precisely this moderate enlargement is the result of hyperthyroidism. Definite conclusions, however, are not possible regarding a group of patients with so many doubtful types of conditions.

## CONCLUSIONS

Hyperthyroidism per se does not cause enlargement of the cardiac area.

When a patient with hyperthyroidism has an enlarged cardiac area, it must be assumed that this is due to some other cardiovascular disease that is also present.

Hyperthyroidism can cause enlargement of the cardiac area when there is associated cardiovascular disease.

Recovery from hyperthyroidism in such cases may be accompanied with a decrease in the size of the heart, and apart from these cases, recovery from hyperthyroidism is not accompanied with changes in the cardiac area.

The bulging of the left middle arch that is frequently encountered in patients with hyperthyroidism is of constitutional origin and is not a result of hyperthyroidism.

51. Stewart, H., and Hamilton, C.: The Effect of Regular and Irregular Tachycardias on the Size of the Heart, J. Clin. Investigation **3**:483, 1927.

# EXOPHTHALMIC GOITER

## RELATION BETWEEN THE BLOOD IODINE LEVEL AND THE DURATION OF SYMPTOMS IN THREE HUNDRED AND FIVE CASES

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AND
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Recent investigations concerning the quantitative estimation of the iodine content of the blood have led to a better understanding of the metabolism of iodine in goitrous conditions. Evidence has been brought forward to show that the iodine level of the blood is elevated in approximately 70 per cent of the cases of clinical hyperthyroidism; in the remaining 30 per cent the level is within the range of normal.[1] In former communications [2] the observation was made that in the greater proportion of cases of hyperthyroidism in which the iodine content of the blood was normal the response to therapy was less favorable than in the cases in which the iodine content was elevated. The duration of hyperthyroidism is recognized clinically as influencing the therapeutic response, in that patients with thyrotoxic symptoms of long standing usually react less favorably to treatment than do those with a history of recent onset of these symptoms. On the basis of the foregoing clinical and laboratory evidence, it seemed reasonable to hypothesize a relation between the concentration of iodine in the blood and the duration of the syndrome of hyperthyroidism. The purpose of the present study was to ascertain whether this supposition was tenable.

### METHOD OF STUDY

One must concede that clinical opinion is subject to variation concerning the duration of hyperthyroidism in many cases. For this reason only those cases were included in which there was agreement with

From the Research Foundation and the Department of Surgery, the Lahey Clinic.

1. Perkin, H. J.; Lahey, F. H., and Cattell, R. B.: Blood Iodine Studies in Relation to Thyroid Disease: Basic Concept of the Relation of Iodine to the Thyroid Gland; Iodine Tolerance Test, New England J. Med. **214**:45 (Jan. 9) 1936.

2. Perkin, H. J.: The Value of Blood Iodine Estimation in the Diagnosis of Hyperthyroidism, S. Clin. North America **15**:1625 (Dec.) 1935; The Value of Blood Iodine Estimations in the Treatment of Clinical Hyperthyroidism, ibid. **16**:1509 (Dec.) 1936.

respect to the onset of the initial symptoms. In the majority of cases the criteria used to establish the time of onset of the disability were a history of loss of weight, associated with a good appetite; hyperexcitability and irritability; protrusion of the eyes; tremor; palpitation, and dyspnea dating from a known experience. Continued loss of weight following the use of a reducing diet or mental stress due to a specific incident was considered to designate the initiatory phase in a few instances.

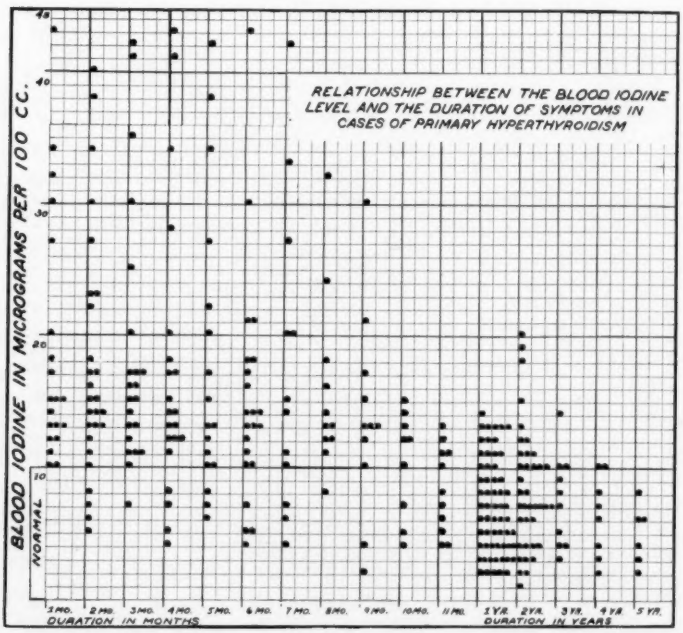
RELATIONSHIP BETWEEN THE BLOOD IODINE LEVEL AND THE DURATION OF SYMPTOMS IN CASES OF PRIMARY HYPERTHYROIDISM
BLOOD IODINE IN MICROGRAMS PER 100 CC.
40
30
20
10
NORMAL
1 MO. 2 MO. 3 MO. 4 MO. 5 MO. 6 MO. 7 MO. 8 MO. 9 MO. 10 MO. 11 MO. 1 YR. 2 YR. 3 YR. 4 YR. 5 YR.
DURATION IN MONTHS
DURATION IN YEARS

Chart showing the relation between the blood iodine level and the duration of symptoms in 305 cases of primary hyperthyroidism.

The series of 305 patients (267 women and 38 men) included in the present report was comprised exclusively of patients with primary hyperthyroidism (exophthalmic goiter). None of the patients, so far as could be determined, had received iodine or other treatment prior to coming under observation at the clinic. The provisional clinical diagnosis of hyperthyroidism was substantiated in every case by basal metabolic tests when the patient was admitted to the hospital and during preoperative medication with iodine, by the histopathologic appearance of the excised thyroid tissue and by examination three months after operation. Before treatment was begun, blood was collected for iodine analysis.

From the data collected, the iodine level of the blood was plotted against the duration of symptoms in individual cases.

RESULTS OF STUDY

Analysis of the results, as shown in the accompanying chart, indicated that the duration of the symptoms of hyperthyroidism varied from one month to five years. Although the distribution of cases was not uniform throughout the entire period, there was considered to be a representative number at each monthly interval to one year and at each yearly interval to five years.

From the accompanying chart it will be seen that of the 163 cases in which symptoms of hyperthyroidism had been present up to nine months, the iodine content of the blood was elevated in 141 (86 per cent) and normal in 22 (14 per cent).[3] Approximately half the values fell within the normal range in cases in which the duration of the symptoms was from nine to eleven months. Of the 122 cases in which

*Summary of Data*

| Duration of Symptoms, Months | Number of Cases | Average Basal Metabolic Rate, % | Average Iodine Content, Micrograms, per 100 Cc. |
|---|---|---|---|
| 1 | 20 | +48 | 18.8 |
| 2 | 27 | +52 | 18.0 |
| 3 | 22 | +50 | 17.5 |
| 4 | 21 | +50 | 17.0 |
| 5 | 17 | +41 | 15.0 |
| 6 | 22 | +45 | 15.5 |
| 7 | 12 | +42 | 16.0 |
| 8 | 11 | +44 | 14.6 |
| 9 | 11 | +47 | 14.0 |
| 10 | 9 | +43 | 11.0 |
| 11 | 11 | +46 | 9.7 |
| 12 | 60 | +45 | 8.8 |
| 24 | 38 | +42 | 8.7 |
| 36 | 10 | +44 | 8.2 |
| 48 | 8 | +38 | 8.3 |
| 60 | 6 | +43 | 7.4 |

symptoms of hyperthyroidism had been present for one year or longer, the iodine content was elevated in 36 (29 per cent) and normal in 86 (71 per cent).

The foregoing findings are considered to indicate a tendency for the iodine content of the blood to be within the normal range in cases in which symptoms of hyperthyroidism had been present for one year or longer. The generalization might be drawn that the iodine level decreases as the duration of hyperthyroidism increases. Corroborative evidence in favor of this view is illustrated by averaging the iodine values and the metabolic rates for each group of cases at each time period (table).

As seen in the accompanying table the average basal metabolic rates were roughly within the same range of elevation throughout the

3. According to the methods previously described (Perkin, H. J.: Determination of Iodine in Blood, Biochem. J. **27**:1078, 1933), 10 micrograms of iodine per hundred cubic centimeters of whole blood is considered to be the upper limit of normal.

entire period. Contrastingly, the average iodine values, which approximated twice normal during the interval of one to four months, fell to a normal level at one year and remained normal throughout the time which followed. The absence of a proportional relation between the degree of elevation of the iodine content and the basal metabolic rate in cases of clinical hyperthyroidism has been noted by others.[4] That a correlation, however, is present between the iodine level and the duration of symptoms apparently has been overlooked.

## COMMENT

Chemical analysis [5] and histologic examination [6] of the excised thyroid tissue in cases of hyperthyroidism in which preoperative iodine medication was or was not given have shown that hyperplastic thyroid tissue is deficient in iodine. The recent investigation of Cole and Curtis [7] has demonstrated the presence of a negative iodine balance in cases of clinical hyperthyroidism. Correlation of the aforementioned studies with the present observations suggests that when the syndrome of hyperthyroidism has been present for one year or longer the iodine content of the blood tends to become normal, in association with a depletion of the iodine reserves of the body.

Since the feeding of thyroid to normal persons effects some of the manifestations characteristic of hyperthyroidism, it is generally assumed that spontaneous hyperthyroidism is related to an excessive amount of secretion from the thyroid gland. In the present study such a view might find application when the iodine level is elevated, as in the cases in which there was a history of short duration. However, it is difficult to conceive that an excessive amount of iodine-containing products is produced by the thyroid gland in cases of hyperthyroidism of long standing when the lack of iodine is evident.

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4. Elmer, A. W., and Scheps, M.: Iodine Content of Blood and of Urine and Basal Metabolic Rate: Their Value in Diagnosis of Function of Thyroid Gland, Acta med. Scandinav. **82**:126, 1934. Curtis, G. M.; Cole, V. V., and Phillips, F. J.: The Blood Iodine in Thyroid Disease, Tr. Am. A. Study Goiter, 1934, p. 142.

5. Cattell, R. B.: The Pathology of Exophthalmic Goitre: Histological and Chemical Study of Changes Following Administration of Iodine (Lugol's Solution), Boston M. & S. J. **192**:989 (May 21) 1925.

6. Marine, D., and Lenhart, C. H.: Further Observations on the Relation of Iodine to the Structure of the Thyroid Gland in the Sheep, Dog, Hog and Ox, Arch. Int. Med. **3**:66 (Feb.) 1909. Cattell, R. B.: The Relation of Iodine to the Human Thyroid Gland in Certain of Its Pathological States with Especial Reference to the Changes in Exophthalmic Goitre After Lugol's Administration, Proc. New York Path. Soc. **25**:128, 1925.

7. Cole, V. V., and Curtis, G. M.: Human Iodine Balance, J. Nutrition **10**: 493 (Nov.) 1935.

On the basis of hypersecretion from the thyroid gland manifested in cases in which the iodine content of the blood is elevated, the favorable response to subtotal thyroidectomy is apparent. Further explanation is necessary with regard to a similar response in cases in which the thyroid gland is deficient in iodine and the iodine content of the blood is normal. Since in many cases the syndrome of clinical hyperthyroidism cannot be attributed solely to hypersecretion of iodine-containing products from the thyroid gland, other factors must be considered.

SUMMARY

The iodine level of the blood has been correlated with the duration of the symptoms in 305 cases of primary hyperthyroidism (exophthalmic goiter) in which treatment had not been given.

The iodine level of the blood is elevated in the majority of cases of hyperthyroidism in which symptoms have been present from one to nine months.

The iodine level tends to fall within the normal range when the syndrome of clinical hyperthyroidism has been present for one year or longer.

The theoretical aspects of the present results have been discussed.

# PAPILLEDEMA ASSOCIATED WITH SUBARACHNOID HEMORRHAGE

## AN EXPERIMENTAL AND CLINICAL STUDY

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AND

W. E. FRY, M.D.

PHILADELPHIA

Papilledema occurs in many but not all cases of increased intracranial pressure. Satisfactory criteria have not as yet been established to differentiate between cases of increased cerebrospinal fluid pressure in which papilledema occurs and those in which it does not. Efforts to set up such criteria follow one of two lines: (1) The important factor is the degree of the intracranial hypertension and its duration. (2) The important factor has to do with the mechanism of the production of papilledema.

The present study deals with the occurrence of papilledema in cases of subarachnoid hemorrhage. During the past seven years this diagnosis has been made for eleven patients in the medical wards of this hospital (table 1). In all these cases bloody or xanthochromic spinal fluid was found. In eight cases the pressure was recorded as ranging from 220 to 400 mm. of water. In the three other cases readings of the manometric pressure were not obtained, but the pressure was thought to be increased. The eyegrounds have been carefully observed in these cases at intervals after the original attack varying from four days to four years, and in no instance has there been papilledema. We believe that the level of the spinal fluid pressure and the duration of observation have been sufficient for papilledema to have occurred if indeed its appearance depends only on factors of pressure and time.

It has been possible to collect from the literature reports of one hundred and eighteen cases of subarachnoid hemorrhage in which satisfactory ophthalmoscopic examinations were recorded.[1] The disks were

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From the Robinette Foundation, the Medical Clinic of the Hospital, the Department of Ophthalmology and the Pepper Laboratory of the University of Pennsylvania.

1. (*a*) Leopold, S.: Spontaneous Subarachnoid Hemorrhage, J. A. M. A. **63**:1362 (Oct. 17) 1914. (*b*) Neal, J. B.: Spontaneous Meningeal Hemorrhage, ibid. **86**:6 (Jan. 2) 1926. (*c*) Symonds, C. P.: Spontaneous Subarachnoid Hemor-

*(Footnote continued on next page)*

normal in seventy-eight (66 per cent) of these one hundred and eighteen cases, and papilledema was recorded as definitely present in twenty-four cases (20 per cent). The condition in the remaining sixteen cases (14 per cent) must be regarded as equivocal. They include cases regarding which such statements as the following were made: "There was a faint suggestion of beginning choking at the nasal border of the left disk." "The disks were hazy, probably slightly beyond physiologic limits." In cases in which the findings were listed as equivocal, one must conclude that the authors were uncertain as to whether papilledema was actually present or not. Information with respect to readings of the manometric pressure of the spinal fluid or duration of observation is not adequate to permit analysis of these cases further. However, we have attempted to consider in more detail the cases in which papilledema was definitely

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rhage, Quart. J. Med. **18**:93 (Oct.) 1924. (*d*) White, W. H.: Two Cases of Intracranial Aneurysm in Young Adults, Tr. Clin. Soc. London **28**:5, 1895. (*e*) Doubler, F. H., and Marlow, S. B.: Hemorrhage into Optic Nerve, Arch. Ophth. **46**:533 (Nov.) 1917. (*f*) Weber, F. P., and Bode, O.: Spontaneous Subarachnoid Hemorrhage with Recovery, J. Neurol. & Psychopath. **7**:39 (July) 1926. (*g*) Duncan, D. H., and Mathews, W. R.: Spontaneous Subarachnoid Hemorrhage, New Orleans M. & S. J. **86**:804 (June) 1934. (*h*) Subarachnoid Hemorrhage, Cabot Case 20171, New England J. Med. **210**:918 (April 26) 1934. (*i*) Laurent, L. P. E.: Spontaneous Subarachnoid Hemorrhage, Clin. J. **62**:330 (Aug.) 1933. (*j*) Hyland, H. H.: Spontaneous Subarachnoid Hemorrhage, Canad. M. A. J. **29**:145 (Aug.) 1933. (*k*) Page, J. A.: Spontaneous Arachnoid Hemorrhage, Lancet **1**:637 (March 25) 1933. (*l*) Russel, C. K.: Spontaneous Subarachnoid Hemorrhage, Canad. M. A. J. **28**:133 (Feb.) 1933. (*m*) Schwenkenberg, A. J.: Spontaneous Subarachnoid Hemorrhage, Texas State J. Med. **28**:814 (April) 1933. (*n*) Shaw, M. E.: Spontaneous Subarachnoid Hemorrhage from Congenital Intracranial Aneurysm, Lancet **1**:138 (Jan. 21) 1933. (*o*) Douglas-Wilson, H.; Miller, S., and Watson, G. W.: Spontaneous Subarachnoid Hemorrhage of Intraspinal Origin, Brit. M. J. **1**:554(April 1) 1933. (*p*) Fuller, H.: Spontaneous Subarachnoid Hemorrhage, J. Florida M. A. **19**:168 (Oct.) 1932. (*q*) Blackford, S. D.: Spontaneous Subarachnoid Hemorrhage, Virginia M. Monthly **59**:1 (April) 1932. (*r*) Dyson, J. E.: Spontaneous Subarachnoid Hemorrhage in Childhood, J. Iowa M. Soc. **22**:223 (May) 1932. (*s*) Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage, Arch. Neurol. & Psychiat. **27**: 1080 (May) 1932. (*t*) Laederich, L.; Favory, A., and Mamou, H.: Un cas d'hémorragie méningée compliquée d'hémorrhagie des gaines du nerf optique, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:616 (April 14) 1930. (*u*) Cubitt, A. W.: Spontaneous Subarachnoid Hemorrhage with Korsakoff's Psychosis, Brit. M. J. **2**:212 (Aug. 9) 1930. (*v*) Riddoch, G., and Goulden, C.: Relationship Between Subarachnoid and Intraocular Hemorrhage, Brit. J. Ophth. **9**:209 (May) 1925. (*w*) Cookson, H.: Spontaneous Subarachnoid Hemorrhage, Brit. M. J. **1**:555 (April 1) 1933. (*x*) Hall, A. J.: Spontaneous Subarachnoid Hemorrhage, Lancet **1**:1135 (May 28) 1932. (*y*) McIver, J., and Wilson, G.: Spontaneous Subarachnoid Hemorrhage, J. A. M. A. **93**:89 (July 13) 1929. (*z*) Byers, R. K., and Hass, G. M.: Thrombosis of Dural Venous Sinuses in Infancy and in Childhood, Am. J. Dis. Child. **45**:1161 (June) 1933.

present, and these will be taken up again later. At this point it may be concluded that (1) papilledema did not occur in our eleven cases, though the degree of elevation of the intracranial pressure and the period of observation appeared adequate, and that (2) it did not occur in a considerable percentage (66 per cent) of the cases reported in the literature.

An experimental approach to the problem was undertaken. It is possible to produce subarachnoid hemorrhage in the rat by thrusting a needle through one of the cranial sinuses. When the skin is retracted, the superior longitudinal and lateral sinuses are visible through the thin skull cap. This method was described in a previous publication on the staining qualities of red blood cells in spinal fluid.[2] After the

TABLE 1.—*Data Concerning Eleven Cases of Subarachnoid Hemorrhage*

| Patient No. | Age | Sex | Previous Attack | Duration of Observation After Attack | Spinal Fluid | Blood Pressure, Mm. Hg | Outcome | Diagnosis Confirmed at Autopsy | Eye-grounds |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 29 | M | No | 8 days | Bloody | 122/ 72 | Died | Yes | Normal |
| 2 | 70 | M | No | 17 days | Xantho-chromic | 140/ 65 | Recovered | .... | Normal |
| 3 | 44 | M | Yes | 4 yr. | Bloody | 125/ 90 | Recovered | .... | Normal |
| 4 | 74 | F | No | 5 days | Bloody | 220/114 | Died | No | Normal |
| 5 | 42 | F | No | 20 days | Bloody | 145/ 90 | Died | No | Normal |
| 6 | 56 | M | Yes | 10 days | Bloody | 186/ 90 | Recovered | .... | Normal |
| 7 | 56 | M | No | 8 days | Bloody | 130/ 90 | Died | No | Normal |
| 8 | 44 | M | No | 7 days | Bloody | 120/ 70 | Recovered | .... | Normal |
| 8 | 45 | M | Yes | 2 hr. | Bloody | ..... | Died | Yes | Not examined |
| 9 | 57 | F | No | 10 days | Bloody | 152/ 90 | Recovered | .... | Normal |
| 10 | 43 | M | No | 6 days | Bloody | 125/ 85 | Died | Yes | Normal |
| 11 | 54 | M | No | 4 days | Bloody | 195/115 | Died | No | Normal |

production of such a hemorrhage, red blood cells are found in abundance in fluid obtained by cisternal puncture for forty-eight hours or more after the operation.

The rationale of our further experimental procedure is based on work previously reported.[3] The principal points may be summarized as follows: 1. Injection of a suspension of colloidal kaolin into the cisterna magna of a normal albino rat causes: (*a*) an increased spinal

2. Griffith, J. Q., Jr.: Roberts, E., and Jeffers, W. A.: Staining Technique for Blood in Spinal Fluid, J. Lab. & Clin. Med. **21**:1208 (Aug.) 1936.

3. Griffith, J. Q., Jr.; Jeffers, W. A., and Lindauer, M. A.: Study of Mechanism of Hypertension Following Intracisternal Kaolin Injection in Rats, Am. J. Physiol. **113**:285 (Oct.) 1935. Griffith, J. Q., Jr.; Jeffers, W. A.; Fewell, A. G., and Fry, W. E.: Communication and Direction of Flow Between Cerebrospinal Fluid and Optic Discs in the Rat, Am. J. Ophth. **20**:457 (May) 1937. Jeffers, W. A.; Griffith, J. Q., Jr.; Fry, W. E., and Fewell, A. G.: An Experimental Study of Choked Disc in the Rat, ibid. **20**:881 (Sept.) 1937.

fluid pressure, ranging from 260 to 300 mm. of water, as compared with the normal of less than 100 mm., and (*b*) a vascular hypertension of 170 to 300 mm. of mercury, as compared with a normal blood pressure of less than 150 mm.

2. Such rats, called for convenience kaolin-hypertensive rats, show no changes in the fundus on ophthalmoscopic or slit lamp examination or on histologic section of the eye.

3. If colloidal thorium dioxide is injected into the cisterna magna of a normal rat, in thirty minutes it can be seen roentgenographically (*a*) in the cervical lymph nodes and (*b*) along the optic tracts and nerves after decapitation and after decalcification of the skull. On histologic examination it is found to lie in the perineural space of the optic nerve.

4. If thorium dioxide is injected into the cisterna magna of a kaolin-hypertensive rat, it does not pass in sufficient quantities to appear in roentgenograms taken either of the cervical lymph nodes or of the optic nerves but remains indefinitely in the cerebrospinal space and ventricles, where it is visible roentgenographically. On histologic study it is either absent from the perineural space of the optic nerve or present in greatly diminished quantity.

5. If a sarcoma is implanted successfully into the cerebellum of a normal rat, changes will occur in the eyes as follows: (*a*) On ophthalmoscopic examination the veins are greatly distended, and there is a suggestion of edema of the disk. This is difficult to evaluate because of the absence of pigment in the albino and, in addition, because the frequent corneal haze makes examination difficult. (*b*) By slit lamp examination of the enucleated eye with the contents removed the elevation of the disk is confirmed. (*c*) By histologic section the venous engorgement and the appearance of edema are confirmed. This condition is thought by us to correspond to papilledema in man.

6. When a similar tumor is implanted into a kaolin-hypertensive rat, no fundal changes occur.

We have therefore concluded that kaolin in the cerebrospinal space (1) blocks the passage of thorium dioxide along the perineural space of the optic nerve and (2) prevents the occurrence of fundal changes even in the presence of a growing tumor of the brain. We believe the evidence justifies the assumption that, at least in the rat, papilledema cannot occur if the perineural space is not patent and that a test for this patency is the ability of thorium dioxide, introduced into the cistern, to enter this perineural space in considerable amounts. We believe that red blood cells in the cerebrospinal fluid might act like kaolin in blocking the perineural space.

### EXPERIMENTAL METHOD

Twenty normal albino rats were used. With the animal under ether anesthesia, a small trephine opening was made over the superior longitudinal sinus. A fine needle was inserted through the sinus to a depth of about 2 mm. and withdrawn. Free external bleeding occurred. Six of the animals had a single subarachnoid hemorrhage, while fourteen had three hemorrhages at three day intervals. Ophthalmoscopic examination was made at intervals. All were finally given an intracisternal injection of thorium dioxide, six at the end of the fourth day and fourteen at the end of the tenth day. The thorium dioxide was given as follows: With the animal under ether anesthesia, cisternal puncture was performed, and 0.05 cc. of spinal fluid was withdrawn. An equal amount of thorium dioxide was injected. At the end of twenty-four hours the animal was killed and decapitated. The head was cleaned and placed in 3 per cent hydrochloric acid for three days. Roentgenograms were then taken.

### EXPERIMENTAL RESULTS

Ophthalmoscopicaly, the fundi were normal. The results of the roentgenographic study are shown in table 2. We know that all the

TABLE 2.—*Data Concerning Twenty Rats in Which Experimental Subarachnoid Hemorrhage Was Induced, Followed by an Intracisternal Injection of Thorium Dioxide*

| Procedure | Number of Animals | Number with Optic Nerves Visualized | Number with Optic Nerves Not Visualized |
|---|---|---|---|
| One subarachnoid hemorrhage | 6 | 2 | 4 |
| Three subarachnoid hemorrhages | 14 | 3 | 11 |
| Totals | 20 | 5 | 15 |

injections were successful, because the thorium dioxide could be seen about the cerebellum. In only five cases, however, did it pass to the optic nerves. In twenty normal animals the thorium dioxide would have been seen about the optic nerves in every case.

Figure 1 *A* is a roentgenogram of the decalcified skull of a rat that had received no thorium dioxide. Figure 1 *B* is a roentgenogram of the decalcified skull of a rat given thorium dioxide intracisternally one hour before death. Note the fine lines of thorium dioxide about the cerebellum and the optic nerves (indicated by arrows). Figure 2 is a roentgenogram of the decalcified skull of a rat given thorium dioxide intracisternally twenty-four hours before death. This rat had three subarachnoid hemorrhages at three day intervals, the last one being induced four days before the injection of thorium dioxide. Lines of thorium dioxide appear about the cerebellum and about the olfactory nerves but not about the optic nerves.

Figure 3 is a photomicrograph of the perineural space of the optic nerve of a rat twenty-four hours after experimental subarachnoid hemorrhage. The space contained many red blood cells.

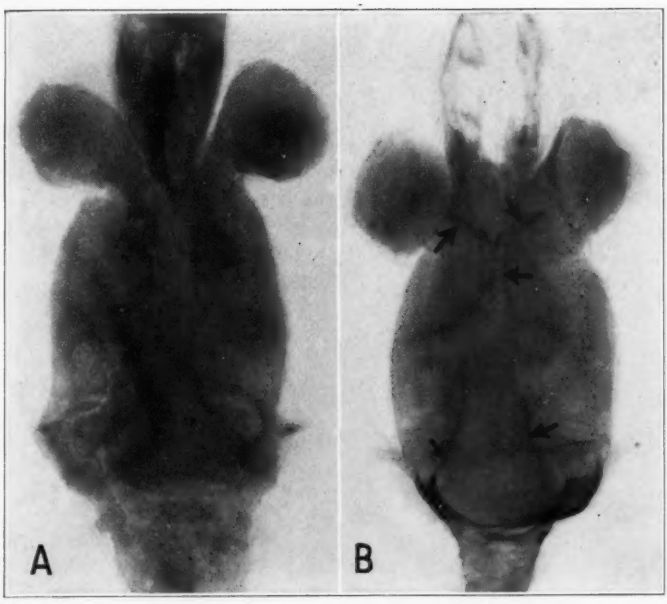


Fig. 1.—*A*, roentgenogram of the decalcified skull of a rat that had not received thorium dioxide. *B*, roentgenogram of the decalcified skull of a rat given thorium dioxide intracisternally one hour before death. Lines of thorium dioxide about the cerebellum and along the optic nerves are indicated by arrows.

Fig. 2.—Roentgenogram of the decalcified skull of a rat given thorium dioxide twenty-four hours before death. This rat had three subarachnoid hemorrhages. Lines of thorium dioxide about the cerebellum and along the olfactory nerves are indicated by arrows. The optic nerves are not shown.

COMMENT

The evidence presented suggests that red blood cells in the cerebrospinal fluid can block the perineural space of the optic nerve to thorium dioxide exactly as does kaolin though not as consistently. Although the manipulation was identical in all cases, the amount of blood which actually entered the cerebrospinal space may have varied widely. If the block were a physical one, depending on the number of red blood cells, we would anticipate that it would not be complete in

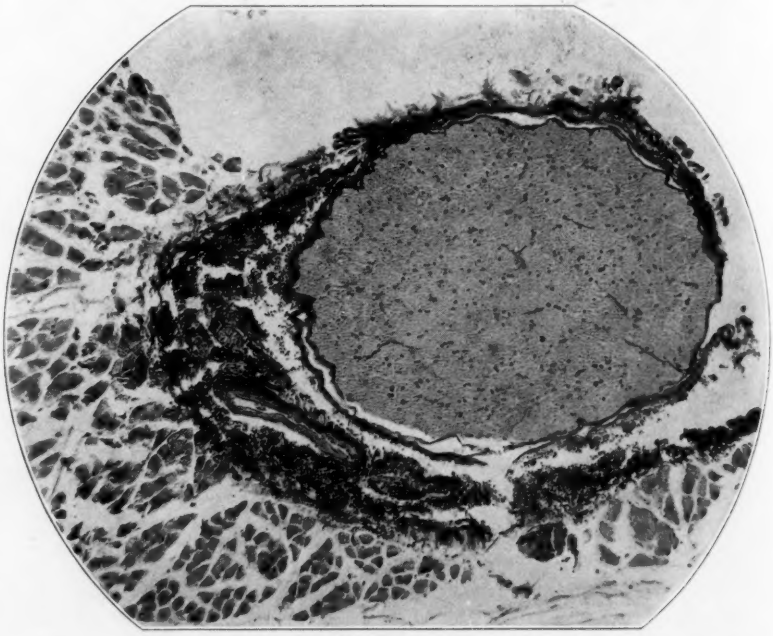

Fig. 3.—Photomicrograph of the perineural space of the optic nerve of a rat twenty-four hours after experimental subarachnoid hemorrhage. The space contains many red blood cells.

all cases. In line with this thought is the evidence that block is more often complete in cases in which there have been three hemorrhages than in those in which there has been one, though the series is too small to make this absolutely certain.

If, based on the evidence previously described, the patency of the perineural space of the optic nerve to thorium dioxide indicates the ability to acquire papilledema, we might expect that in fifteen of our twenty animals with subarachnoid hemorrhage choked disk could not

have developed even if added factors which ordinarily cause choking had been present. On the other hand, we might expect that in five of our twenty animals papilledema would have developed if other factors which ordinarily produce choking had been present coincidentally.

In reviewing further the twenty-four cases of subarachnoid hemorrhage with definite papilledema reported in the literature, we find the following data: 1. The blood pressure was high in ten cases. In three of these the diagnosis was confirmed at autopsy. 2. The blood pressure was normal in one case, the diagnosis being confirmed at autopsy. 3. The blood pressure was not given in thirteen cases. In seven of these there was no autopsy. In the six cases in which autopsy was performed the diagnosis was confirmed in three, in two cases glioma was found and in one case there was a large unruptured aneurysm which was thought to have acted like a tumor.

It appears to be rare for definite papilledema to occur in a case of proved uncomplicated subarachnoid hemorrhage. Among the complications which might occur and cause papilledema are (1) a hemorrhage largely into the ventricles, with only a little blood reaching the subarachnoid space, (2) malignant hypertension, (3) glioma and (4) sinus thrombosis.

## REPORT OF CASES

*Hemorrhage into the Ventricles.*—Cookson [1w] has reported the case of a man of 32 who had an attack of headache, pain in the neck and vomiting on July 4, 1924. He remained in bed two weeks, when he again vomited, became unconscious and was taken to the hospital. When admitted he was semiconscious and irritable. There was palsy of the right facial nerve and an extensor plantar reflex on the right side. Cervical rigidity and a definite Kernig sign were noted. The cerebrospinal fluid was blood stained. The fundi oculi were normal on entry, but shortly afterward papilledema appeared in both eyes and later became severe. He improved somewhat, but eleven days after admission to the hospital he suddenly went into a coma and died the next day. At autopsy a blood clot was seen adherent to the left internal carotid artery at the point of its bifurcation. In this region the brain tissue was ploughed up, and blood clot filled the left lateral, third and fourth ventricles.

*Cerebral Hemorrhage Involving the Subarachnoid Space in the Course of Malignant Hypertension.*—The patient, a Negro 45 years of age, had been well until five years prior to admission to the hospital. At that time he was told he had high blood pressure, the systolic pressure being 240 mm. He continued in fair health until two years before admission to the hospital, when he noted some failing of vision. About this time he began to have attacks of unconsciousness, lasting about five minutes, which recurred irregularly but on the average of about once a month. Some convulsive movements during an attack were described by his wife. However, the attacks were always of short duration, and he recovered rapidly, never requiring hospitalization. His physician stated that for at least a year prior to admission to the hospital he had definite bilateral papilledema.

On the day of entry the patient suddenly had a generalized convulsion, lost consciousness and was admitted to this hospital in coma, which persisted until his

death. The blood pressure was 260 systolic and 160 diastolic. The pupils did not react to light. The fundus of the right eye showed numerous old and new hemorrhages and fairly marked evidence of angiosclerosis. The disk showed definite slight papilledema. The fundus of the left eye was similar. Spinal puncture, thrice repeated, revealed bloody fluid under increased pressure. The patient died two days after admission to the hospital. At autopsy a cerebral hemorrhage was seen involving the right occipital lobe, with blood in the subarachnoid space. The right ventricle was dilated and filled with blood. The bleeding point could not be ascertained.

*Subarachnoid Hemorrhage Complicated by a Glioma* (reported by Laurent [11]).—A man aged 26 was admitted to the hospital on April 11, 1931. For two weeks he had complained of headache and vomiting. On April 7 he vomited and lost consciousness. Violent convulsive movements of the right arm occurred, while the left limb and left side of the face seemed to be paralyzed. He recovered to some extent but remained stuporous.

On entry he was comatose, and the temperature was 100.6 F. The fundus oculi bilaterally showed papilledema. There were cervical rigidity, a definite Kernig sign and flexor plantar responses. The cerebrospinal fluid was evenly blood stained. The next day he recovered sufficiently to enjoy an illustrated magazine. On April 13 he again became comatose and died. Necropsy revealed a large hemorrhage originating from a glioma and reaching the surface of the frontal lobe.

*Sinus Thrombosis and Subarachnoid Hemorrhage* (reported by Byers [12]).—A girl aged 1 year who had previously been healthy began to vomit on Oct. 16, 1931. The next day a physical examination showed no abnormality. Diarrhea developed. Two days later there were convulsive twitchings of the right arm, followed by generalized convulsions. She then appeared to improve, but on the eleventh day of her illness she was drowsy and irritable. The following day there were rhythmic convulsive moments of the legs and rigidity of the neck, back and extremities. The spinal fluid was xanthochromic and under increased pressure. Generalized convulsions soon developed. Within a few hours engorgement of the facial veins, edema of the left eyelids and a bulging fontanelle became evident. The eyegrounds showed edema of the optic disks and congestion of the retinal veins. Convulsions continued, and death occurred on the fourteenth day. At necropsy there was seen in the superior longitudinal sinus a thrombus with extensions into the contiguous sinuses and veins.

## SUMMARY

Papilledema did not occur in any of the eleven cases of subarachnoid hemorrhage studied, although the elevation of the spinal fluid pressure and the duration of observation appeared adequate. In seventy-eight (66 per cent) of the one hundred and eighteen cases reported in the literature papilledema did not develop. In this series, the findings in sixteen cases (14 per cent) were equivocal, while in twenty-four cases (20 per cent) definite papilledema developed. In seven of these twenty-four cases the diagnosis was confirmed at autopsy, and in three of these cases hypertension was known to have been present. In two other cases glioma of the brain was found, and in one case a large unruptured aneurysm was thought to have acted like a tumor.

In previous work it was shown that kaolin injected intracisternally into rats (1) prevented the passage of thorium dioxide, injected intracisternally, along the perineural spaces of the optic nerves and (2) prevented the appearance of papilledema in the presence of a growing cerebellar tumor. After experimental subarachnoid hemorrhage, thorium dioxide was blocked from entering the perineural spaces of the optic nerves in fifteen of twenty rats. It was therefore inferred that blood in the spinal fluid if present in sufficient amount tends to block the perineural spaces of the optic nerves and prevent the development of papilledema. In a minority of cases, however, the block is incomplete, and papilledema may occur if other predisposing factors are present. Among these factors are (1) a partial ventricular block, so that relatively little blood reaches the subarachnoid space, (2) malignant hypertension, (3) glioma and (4) sinus thrombosis. Illustrative cases are cited.

# COEXISTENCE OF BRONCHIECTASIS AND SINUSITIS

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The frequent coexistence of bronchitis and bronchiectasis with sinusitis has been recognized since the publication of the reports of Rist [1] and Sergent,[2] and confirmation of their observations has been offered repeatedly. This association is well known to otolaryngologists, but appreciation by general practitioners and specialists in other fields has lagged surprisingly. The relation between the disease of the upper and that of the lower respiratory tract is more than coincidental in the opinion of most observers. Whether the sinusitis precedes, follows or develops simultaneously with the bronchitis is not settled. The prevailing concept is that sinusitis and bronchitis probably develop simultaneously during an acute infection, such as influenza. Mullin [3] gave as his opinion that patients with bronchitis tend to get well unless the condition is fostered and fed by a chronic sinus infection. This appears to be logical. Rist [1] compared the respiratory tract to the urinary tract, in which cystitis follows renal infection. Mullin [3] offered as explanation for the concomitant lesions the repeated aspiration of infective material into the bronchi from the upper respiratory tract. He objected to the concept of infection spreading from the bronchi to the sinuses because there is no ready route and because of the great number of patients, especially children, with cough and moist rales at the bases

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1. Rist, E.: Le principes du diagnostic rationnel de la tuberculose pulmonaire, Presse méd. **24**:305, 1916; Les diagnostic différentiel de la tuberculose pulmonaire et les affections chroniques des fosses nasales, ibid. **24**:321, 1916.

2. Sergent, E.: Histoire suggestive de quelques faux tuberculeux, diagnostic différentiel de la tuberculose pulmonaire et des affections des voies respiratoires supérieures, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1424, 1916; Considerations sur la statistique du centre de triage, la Charité le Vésinet, de Juin 1916 à Décembre 1917, J. de méd. et chir. prat. **89**:643, 1918.

3. Mullin, W. V.: The Accessory Sinuses as an Etiologic Factor in Bronchiectasis, Ann. Otol., Rhin. & Laryng. **30**:683, 1921: A Review of Sinus-Chest Infections, ibid. **41**:794, 1932.

of the lungs who get well after early diagnosis of the condition and treatment of the sinuses. Wasson and Waltz [4] drew similar conclusions from roentgen findings for children with sinus infection and pulmonary disease.

In experimental animals Mullin and Ryder [5] demonstrated aspiration of ink and suspensions of tubercle bacilli from the nares and the antrum into the bronchial tree. After the introduction of india ink they observed black spots all along the respiratory tract post mortem, with discoloration of the bronchial nodes and of the lungs. Aspiration of tubercle bacilli resulted in tuberculosis of the lungs. Involvement of the lungs followed instillation of the bacilli or india ink into the antrum, even though egress to the nares was prevented. This was explained on the basis of a lymphatic and venous route to the right side of the heart and then to the lungs. Corper and Robin [6] confirmed and amplified these results in their study of dogs and rabbits.

Quinn and one of us (Dr. Meyer) [7] ascertained that when iodized oil was passed through a catheter just into the anterior nares of a sleeping individual, the oil, often in large quantities, was demonstrable roentgenographically in the bronchi or in the pulmonary parenchyma the next morning.[7] This experiment has been confirmed and the conclusion accepted.[8] The ease and regularity of the occurrence led to the conclusion that aspiration of pus probably occurs with similar facility. Consequently, it was thought likely that this was the most important explanatory factor for the frequent concomitance of sinusitis and bronchiectasis. Incidentally, this circumstance emphasized the importance of treatment of sources of pus, the sinuses, as well as treatment of the bronchi in cases of chronic bronchitis and bronchiectasis.

The frequency of sinusitis in association with infection of the bronchi varies with different reports. Thus, Kistner [9] found sinusitis in all but 6 of 196 cases of chronic nontuberculous bronchitis. Dunham

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4. Wasson, W. W., and Waltz, H. D.: The Relationship of Sinus Disease to Chest Disease in Children, Radiology **22**:432, 1934.

5. Mullin, W. V., and Ryder, C. T.: Studies on the Lymph Drainage of the Accessory Nasal Sinuses, Laryngoscope **31**:158, 1921. Mullin, W. V.: Lymph Drainage of the Accessory Nasal Sinuses, ibid. **29**:606, 1919.

6. Corper, H. J., and Robin, H. A.: The Pulmonary Aspiration of Particulate Matter, Am. Rev. Tuberc. **6**:813, 1922.

7. Quinn, L. H., and Meyer, O. O.: The Relationship of Sinusitis and Bronchiectasis, Arch. Otolaryng. **10**:152 (Aug.) 1929.

8. Meakins, J. C.: Practice of Medicine, St. Louis, C. V. Mosby Company, 1936, p. 148.

9. Kistner, F. B.: Infections of Accessory Nasal Sinuses as the Cause of Chronic Non-Tuberculous Bronchitis, Northwest Med. **26**:203, 1927.

and Skavlem [10] found sinusitis coexisting in 73 per cent of 26 cases of bronchitis. McLaurin [11] said he believed that the association of bilateral bronchiectasis and paranasal sinus disease is almost constant. Hodge [12] reported associated sinusitis in 75 per cent of his 37 cases. Meiks,[13] in a study of children, found sinusitis present in 81 per cent of those with bronchiectasis. Quinn and one of us (Dr. Meyer) [7] reported that 22 of 38 patients with bronchiectasis (57.9 per cent) had coexistent sinusitis. The fact was emphasized that the majority of the patients had no symptoms of sinusitis. Kern and Schenck,[14] in a controlled series, found that sinusitis existed less frequently in patients with no history of susceptibility to colds, recent infection of the respiratory tract or frank sinus disease in the past than in patients with bronchiectasis.

The present study was made in order to amplify the study of 38 patients which was reported in 1929.[7] It is now possible to report on the incidence of sinusitis in a total of 217 patients with bronchiectasis admitted to the State of Wisconsin General Hospital between 1925 and 1936, exclusive of patients with congenital bronchiectasis or with bronchiectasis due to foreign body. (One of the 38 cases reported on in 1929 was due to aspiration of a foreign body; the remaining 37 are included in the total number of this report.) It may be stated that in this report as in the previous report, sinusitis was diagnosed only when gross pus was demonstrable in one or more of the paranasal sinuses.

On analysis of this group of 217 patients, it was found that 145 (66.8 per cent) had associated sinusitis. This figure closely approximates the incidence of 57.9 per cent in the first 38 patients studied.

A study of these 145 patients showed that 84 (58 per cent) were males, and 61 (42 per cent) were females. The oldest patient was 78 and the youngest 6 years old. The average age at the time of admission to the hospital was 32.4 years and the average age at the onset of symptoms 26.1 years. However, 49 per cent of the patients admitted

10. Dunham, K., and Skavlem, J. H.: Chronic Non-Tuberculous Infections, U. S. Vet. Bur. M. Bull. **3**:861, 1927.

11. McLaurin, J. G.: Chest Complications of Sinus Disease, Ann. Otol., Rhin. & Laryng. **41**:780, 1932; A Review of the Interrelationship of Paranasal Sinus Disease and Certain Chest Conditions, with Especial Consideration of Bronchiectasis and Asthenia, ibid. **44**:344, 1935.

12. Hodge, G. E.: Relation of Bronchiectasis to Infection of Paranasal Sinuses, Arch. Otolaryng. **22**:537 (Nov.) 1935.

13. Meiks, L. T.: Study of Bronchiectasis with Reference to Its Etiology and Management, Tr. Am. Laryng., Rhin. & Otol. Soc. **41**:421, 1935.

14. Kern, R. A., and Schenck, H. P.: Chronic Paranasal Sinus Infections: Relation to Diseases of Lower Respiratory Tract, Arch. Otolaryng. **18**:425 (Oct.) 1933.

were under 25, and 66.8 per cent were under 40. In 64.8 per cent of the patients the onset of the disease occurred before the age of 30 years. It is noteworthy that in 31 cases the onset antedated the age of 5, although none of the patients in this series was under this age.

Various symptoms and illnesses preceded the apparent onset of the bronchiectasis. In 73 (half the cases) the anamnesis did not permit conclusions as to the possible exciting cause. In 22 of the remaining 72 cases (30.6 per cent) the onset dated from influenza and in 19 (26.4 per cent) from pneumonia. However, the incidence of influenza and pneumonia in the past medical history was greater, although the patients did not relate the symptoms to these illnesses on entry.

The bronchiectasis involved both lungs in 109 cases (75.2 per cent), and the bases alone were involved in 99 (68.3 per cent) of these. In 72 cases (49.7 per cent) the bases were equally involved, in 21 (14.6 per cent) the base of the left lung showed greater involvement than that of the right, while in 6 cases the base of the right lung showed the more extensive disease. In the remaining 36 cases there was unilateral involvement, and as in the original study of 38 cases, there was no predominance of disease of the right lung over that of the left. Thus, involvement of the right and of left lung each occurred in 18 cases (12.4 per cent). This is in direct variance with the common opinion that disease of the right lung occurs more frequently and is more severe.

The degree of bronchiectasis was based on the subjective and objective symptoms, the general constitutional disability, the roentgen findings and, in 5 instances, the postmortem observations. It must be admitted that differences of opinion might here occur in some borderline cases. In 42 cases (29 per cent) there was only mild bronchiectasis; in 81 cases (55.8 per cent), moderately advanced disease, and in 22 cases (15.2 per cent), far advanced disease. Satisfactory filling of the bronchi with iodized oil was possible in 100 of the 145 cases, and roentgenography following this aided in establishment of the existence and of the degree of the disease.

The extent of sinus involvement was variable, and no relation between the degree of sinusitis and the degree of bronchiectasis was established. Chronic pansinusitis or gross bilateral infection of the antrum was found to exist in 78 cases (53.8 per cent).

Satisfactory bacteriologic studies were not always made. However, repeated examinations of sputum for tubercle bacilli were made in 135 of the cases, and the organisms were found in 1 case. The predominant organism in the sputum was not reported in two thirds of the cases; in the remaining cases streptococci predominated, being present in 28 cases. Vincent's organisms were not found in the sputum in 8 of the 10 cases in which they were sought.

*Summary of Data*

| | Bronchiectasis | | | |
|---|---|---|---|---|
| | With Sinusitis | | Without Sinusitis | |
| | Number | Percentage | Number | Percentage |
| Cases | 145 | 66.8 | 72 | 33.2 |
| Males | 84 | 58 | 41 | 57 |
| Females | 61 | 42 | 31 | 43 |
| Average age on entry | 32.4 years | | 35 years | |
| Under age of 25 years | 71 | 49.0 | 26 | 36.1 |
| Under age of 40 years | 97 | 66.8 | 43 | 59.7 |
| Average age at onset | 26.1 years | | 27.5 years | |
| Type of onset (from history) | | | | |
| Unknown | 73 | 50.4 | 29 | 40.3 |
| Influenza | 22 | 15.1 | 7 | 9.7 |
| Pneumonia | 19 | 13.1 | 19 | 26.4 |
| Influenza and pneumonia | .. | .... | 2 | 2.8 |
| Common cold | 14 | 9.6 | 7 | 9.7 |
| Grip | 4 | 2.8 | .. | .... |
| Sinus infection | 2 | 1.4 | .. | .... |
| Measles | 1 | 0.7 | .. | .... |
| Mumps | 1 | 0.7 | .. | .... |
| Scarlet fever | 1 | 0.7 | .. | .... |
| Pertussis | 2 | 1.4 | 1 | 1.4 |
| Diphtheria | 1 | 0.7 | 1 | 1.4 |
| Typhoid | 1 | 0.7 | .. | .... |
| Pleurisy | 1 | 0.7 | 1 | 1.4 |
| Weakness and fever | 1 | 0.7 | .. | .... |
| Shortness of breath | 1 | 0.7 | .. | .... |
| Exposure | 1 | 0.7 | .. | .... |
| "Spitting up blood" | .. | .... | 2 | 2.8 |
| Chill followed by sweating | .. | .... | 1 | 1.4 |
| Asthma | .. | .... | 1 | 1.4 |
| Childbirth | .. | .... | 1 | 1.4 |
| Type of bronchiectasis | | | | |
| Bilateral | 109 | 75.2 | 38 | 52.8 |
| Right lung | 18 | 12.4 | 19 | 26.4 |
| Left lung | 18 | 12.4 | 15 | 20.8 |
| Severity of bronchiectasis | | | | |
| Slight | 42 | 29.0 | 23 | 32.0 |
| Moderately advanced | 81 | 55.8 | 35 | 48.6 |
| Far advanced | 22 | 15.2 | 14 | 19.4 |
| Filling of bronchi with iodized oil | | | | |
| Satisfactory | 100 | 69.0 | 42 | 58.3 |
| Inadequate | 8 | 5.5 | 4 | 5.6 |
| None | 37 | 25.5 | 26 | 36.1 |
| Disease of respiratory tract in past | | | | |
| Influenza | 35 | 24.1 | 13 | 18.0 |
| Pneumonia | 30 | 20.7 | 19 | 26.3 |
| Pleurisy | 4 | 2.8 | 1 | 1.4 |
| Pertussis | 6 | 4.1 | 2 | 2.8 |
| Combination of 2 or more diseases | 33 | 22.8 | 27 | 37.5 |
| None | 37 | 25.5 | 10 | 14.0 |
| Tonsils | | | | |
| Septic | 56 | 38.6 | 33 | 45.8 |
| Atrophic | 18 | 12.4 | 12 | 16.7 |
| Tags | 8 | 5.5 | 6 | 8.4 |
| Removed | 55 | 38.0 | 17 | 23.6 |
| Condition unknown | 5 | 3.4 | 2 | 2.8 |
| Normal | 3 | 2.1 | 2 | 2.8 |
| Predominating organisms in sputum | | | | |
| Unknown | 99 | 68.3 | 42 | 58.4 |
| Streptococci | 28 | 19.3 | 17 | 23.3 |
| Yeast | 6 | 4.1 | 1 | 1.4 |
| Fungi | 4 | 2.8 | 2 | 2.8 |
| Spirochetes and fusiform bacteria | 2 | 1.4 | 3 | 4.2 |
| Gram-positive bacilli | 1 | 0.7 | .. | .... |
| Streptothrix | .. | .... | 1 | 1.4 |
| Gram-positive diplococci | .. | .... | 1 | 1.4 |
| No tubercle bacilli | 135 | 93.1 | 65 | 90.3 |
| Tubercle bacilli | 1 | 0.7 | 2 | 2.8 |
| Not examined | 9 | 6.2 | 5 | 6.9 |
| No fungi | 20 | 13.8* | 5 | 6.9 |
| No spirochetes or fusiform bacilli | 8 | 5.6 | 7 | 9.7 |

* This figure includes some cases of bronchiectasis with sinusitis and all without sinusitis in the foregoing figures.

*Summary of Data—Continued*

| Type of sinusitis | Bronchiectasis | | | |
|---|---|---|---|---|
| | With Sinusitis | | Without Sinusitis | |
| | Number | Percentage | Number | Percentage |
| Pansinusitis | 39 | 26.9 | | |
| Bilateral maxillary and ethmoid | 8 | 5.5 | | |
| Bilateral maxillary and frontal | 6 | 4.1 | | |
| Bilateral maxillary and sphenoid | 1 | 0.7 | | |
| Bilateral maxillary, right ethmoid and sphenoid | 1 | 0.7 | | |
| Bilateral maxillary and right ethmoid | 3 | 2.1 | | |
| Right antrum and frontal | 2 | 1.4 | | |
| Bilateral maxillary and left frontal | 2 | 1.4 | | |
| Bilateral maxillary and right frontal | 1 | 0.7 | | |
| Left antrum, left ethmoid and frontal | 1 | 0.7 | | |
| Left antrum and frontal | 1 | 0.7 | | |
| Bilateral maxillary | 39 | 26.9 | | |
| Right frontal and right antrum | 1 | 0.7 | | |
| Left antrum, right ethmoid | 1 | 0.7 | | |
| Right antrum and right sphenoid | 1 | 0.7 | | |
| Right antrum | 18 | 12.4 | | |
| Left antrum | 13 | 9.0 | | |
| Right frontal | 4 | 2.8 | | |
| Left frontal | 1 | 0.7 | | |
| Left ethmoid | 1 | 0.7 | | |
| Unknown | 1 | 0.7 | | |

In 72 (33.2 per cent) of the 217 patients there was no evidence of sinusitis. As in the group with sinusitis, there was a slight predominance of males, the ratio being 57 to 43. The average age in this group at the time of entry was somewhat higher, 35 years; the range, 8 to 73 years. The average age at onset was also higher, 27.5 years. Twenty-six (36.1 per cent) of the patients were under 25 at the time of admission to the hospital, and 43 (59.7 per cent) were under 40. A significant number of patients—31 (43 per cent)—were under 20 years of age at the time of onset of the disease.

Most of these patients ascribed the onset of bronchiectasis to definite disease or symptoms. Twenty-nine (40.3 per cent) could relate the disease to no cause. Of the remaining 43 patients, 19 (44.2 per cent) dated their illness from pneumonia, whereas only 7 (16.3 per cent) had had preceding influenza. Only 14 per cent of the patients failed to give a history which included disease of the respiratory tract at some time in the past.

Both lungs were involved in 38 (52.8 per cent) of the cases of bronchiectasis without sinusitis, a distinctly lower frequency than in the group of cases of bronchiectasis with sinusitis. In the 34 cases of unilateral bronchiectasis without sinusitis the right lung was involved 19 times and the left lung 15 times.

The degree of bronchiectasis was mild in 23 cases (32 per cent), moderately advanced in 35 (48.6 per cent) and far advanced in 14 (19.4 per cent). Postmortem examination was made in 7 of these cases of bronchiectasis without sinusitis. Satisfactory filling of the bronchi with iodized oil was possible in 42 of the 72 cases.

Examination of the sputum for tubercle bacilli was made in 65 of the 72 cases and showed positive results twice. In 17 of the 30 cases in which the predominating organism in the sputum was reported, it was found to be the streptococcus.

A comparison of the two groups of cases of bronchiectasis (with and without sinusitis) is afforded by study of the accompanying table.

## COMMENT

Study of these results reemphasizes the frequency of sinusitis in association with bronchiectasis. The ease of aspiration of iodized oil from the nares by a recumbent sleeping person makes the factor of repeated infection of the bronchi, which would otherwise heal, by aspiration of pus seem logical. The frequent history of preceding influenza and pneumonia suggests that the bronchi and sinuses may well be infected simultaneously. The cases of bronchiectasis without sinusitis, however, were commonly preceded by influenza, pneumonia or some other infection of the respiratory tract. Consequently, it must be appreciated that bronchiectasis can occur without gross infection of the sinuses. That sinusitis may have previously existed or may have persisted in minimal degree cannot be excluded. Furthermore, disease elsewhere in the upper respiratory tract, as for example in the tonsils, may operate to reinfect the bronchi. Nevertheless, the importance of the sinus infection is not to be minimized, and the opinion is held that in early bronchitis, if disease of the sinuses is recognized and treated, bronchiectasis may, at least occasionally, be prevented. It is well recognized that treatment of the sinuses as well as treatment of the lower respiratory tract is imperative in bronchiectasis if good results are to be obtained.

The relative frequency of bronchiectasis in children is again brought out in this study. The association of sinusitis in this group is especially common, and early recognition and treatment of the sinuses may be of greatest benefit.

Finally, the lack of symptoms of sinusitis in most of the cases here reported is of importance, indicating the need for careful exclusion of disease of the upper respiratory tract by roentgenograms and other available means.

## SUMMARY AND CONCLUSIONS

One hundred and forty-five (66.8 per cent) of 217 patients with bronchiectasis were found to have associated sinusitis.

The majority of these patients had no subjective symptoms of sinusitis.

As a class, the patients with sinusitis were younger than those without.

From this series no definite relation between the degree of sinusitis and the degree of bronchiectasis could be established.

Contrary to general opinion, in cases of bilateral bronchiectasis there was no demonstrable predominance of disease of the right lung, and in cases of unilateral bronchiectasis there was no greater incidence of involvement of the right lung.

It is believed that the relation between sinus disease and disease of the lower respiratory tract is more than coincidental and that drainage from the sinuses, especially when the patient is recumbent and asleep, makes for repetitive infection of the bronchi.

The importance of early diagnosis and treatment of existing sinus disease in cases of bronchitis and bronchiectasis is emphasized.

# ANEURYSM OF THE INNOMINATE ARTERY

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Within recent years, particularly since the development of methods for the intensive treatment of syphilis, aneurysms of the large vessels, on the whole, have not been of as much clinical interest to physicians and students as formerly. Recently a patient with aneurysm of the innominate artery was under my observation. This case perhaps illustrates the potential danger to the patient of vigorous antisyphilitic treatment in association with aneurysm, with its resultant subjective improvement, and also may serve as a gentle reminder that clinicians in the past were thoroughly familiar with aneurysm of this type, that they developed methods of treating such an aneurysm which often were successful and that past experience may well serve as a guide toward improving in the future the methods of treatment when an aneurysm involves this particular vessel.

Curiously, aneurysms of the innominate artery are by no means common. According to Osler [1] and Reid and Andrus,[2] they represent only about 3 per cent of all internal aneurysms. Yet because of their spectacular appearance and course, they have interested clinicians for centuries.

It is said that the earliest mention of aneurysm of the innominate artery in medical literature was made by Antyllus,[3] a surgeon who lived in the middle of the second century A. D. Ambroise Paré [4] (1510-1590) was the first to suggest the causative relation of syphilis and aneurysm, in his famous report of a tailor who while playing tennis "fell dead, the vessel being broken, such as frequently happens to those who have often had the unction and sweat for the cure of the French Disease;" and the clinical diagnosis of ruptured aneurysm was confirmed at a public anatomic demonstration by Paré himself.[5] The story is told of Valsalva,

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From the Evans Memorial for Clinical Research and Preventive Medicine.

1. Osler, W.: Aneurysm, in Modern Medicine, Philadelphia, Lea & Febiger, 1908, vol. 4, chap. 11, p. 448.

2. Reid, M. R., and Andrus, W.: Surgery of the Arteries, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1931, vol. 1, chap. 12, p. 752.

3. Antyllus, cited by Osler.[1]

4. Paré, cited by (*a*) Beekman, F.: Studies in Aneurysm by William and John Hunter, Ann. M. Hist. **8**:126 (March) 1936. (*b*) Major, R. W.: Classic Descriptions of Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 417.

5. Paré, cited by Fitz, R.: A Case of Thoracic Aneurysm, M. Clin. North America **16**:863 (Jan.) 1933.

an Italian physician of the eighteenth century, that he cured patients with aneurysm by starving them. According to Matas,[6] Valsalva once was holding a clinic at Imola on the medical treatment of aneurysm. A poor patient with a large aneurysm of the neck, probably of the innominate or the carotid artery, was one of the subjects of the lecture. The man listened attentively when Valsalva said that in some cases aneurysm can be cured by diet and rest, provided the patient can endure the hardship of treatment. Little sips of water, a few spoonfuls of claret, a dry crust of black bread and a bit of dry meat now and then—just enough to keep body and soul together—with rest flat in bed, that would cure aneurysm in the right sort of case. About six months later Valsalva was surprised to have an emaciated man come and kneel down before him and kiss his coat. Valsalva said, "What is the matter?" To which the patient replied, "Why, don't you know you have saved my life?" "What did you do?" queried Valsalva. "Just what you said," replied the patient. "Just starved and stayed in bed." The aneurysm had subsided, and it no longer pulsated in the neck.

In the nineteenth century the surgical approach to the treatment of aneurysm of the innominate artery first began to attract attention. In 1829 Valentine Mott,[7] of New York, following the suggestion of Mr. James Wardrop,[8] surgeon to the king of England, was the first American surgeon to ligate the right carotid artery in a case of innominate aneurysm.

Such a procedure must have been extremely difficult and hazardous before the days of ether, yet additional cases soon were reported; after the introduction of ether a considerable literature on the surgical treatment of innominate aneurysm developed.

Certain striking cases have been reported. Barwell,[9] in 1877, ligated the right common carotid and right subclavian arteries of a 45 year old laborer, a patient at the Charing Cross Hospital, London, who had an aneurysm at the right of the base of the neck, reaching as far as the cricoid cartilage. Seven weeks after the operation the visible enlargement had decreased and was reduced to about the size of a pigeon's egg, being located behind the right sternoclavicular joint. Autopsy finally verified the presence of a small innominate aneurysm which had

6. Matas, R.: On the Treatment of Aortic Aneurysm by the Method of Jugulo-Carotid Anastomosis: A Discussion, New Orleans M. & S. J. **84**:448 (Dec.) 1931.

7. Mott, V.: Aneurysm of the Arteria Innominata, Involving the Subclavian and the Root of the Carotid, Successfully Treated by Tying the Carotid Artery, Am. J. M. Sc. **5**:297 (Feb.) 1829.

8. Wardrop, J.: On Aneurysm and Its Cure by a New Operation, London, Longman & Co., 1828.

9. Barwell, R.: On Aneurysm, Especially of the Thorax and Root of Neck, London, Macmillan & Co., 1880, pp. 32-77.

shrunken and was sclerosed. In this country Mynter,[10] in 1887, and Gay,[11] in 1897, both performed successful ligations. In 1909 Schwyzer [12] performed distal ligation of the right common cartoid and right subclavian arteries for an innominate aneurysm presenting in the neck. The patient lived at least twenty-two years after the ligation. In this case the tumor also disappeared. A patient with a perforating aneurysm was operated on by Rosenstern [13] and was said to have lived many years. Another case that was remarkable for the long duration of the condition was mentioned by Miller,[14] of London. His patient had an aneurysm of the innominate artery which presented at the base of the neck when he was 41 years old. The aneurysm was treated by injections of quinine hydrochloride and ethyl carbamate and also by ligation of the right common carotid and subclavian arteries when the patient was aged 56. He died at the age of 64 as a result of internal rupture of the aneurysm. In 1929 James Greenough [15] gathered together the literature on operations on the innominate artery. He stated as his belief from the cases reported and his own experience that if the operation is for aneurysm, distal as well as proximal ligation should be done and the sac should be extirpated or destroyed. While among all the 91 reported cases which he collected the mortality after ligation was 56 per cent, when the cases were grouped chronologically it was clear that as surgical methods had improved the operative mortality of this type of operation had diminished. His conclusion was that operation is justifiable and if contemplated should be done early.

The following report is of a case which I had the opportunity of studying.

CASE 1.—The patient was a 64 year old Irishman. Recently he had worked as a day laborer, though in the early days he had been a sailor, roving pretty much all over the world. He entered the hospital on Jan. 15, 1937, complaining of a sizable lump in his neck and of pain in his right shoulder.

When he was 18 years old he had a chancre, which was treated for two years with medicine administered in pill form. This was the only treatment for syphilis that he had received. Eleven years before entry to the hospital he first noticed "neuritis" of the right shoulder. This consisted of a sharp shooting pain which

10. Mynter, H.: Aneurysm of Innominate Artery Treated with Ligation of Right Carotid and Subclavian Arteries, M. Rec. **32**:507, 1887.

11. Gay, G. : A Case of Ligature of Innominate Artery for Aneurysm, Boston M. & S. J. **137**:13, 1897.

12. Schwyzer, A.: Aneurysm of the Innominate Artery, Ann. Surg. **96**:666 (Oct.) 1932.

13. Rosenstern, cited by Osler, W.: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, chap. 22, p. 888.

14. Miller, C.; Dolbey, R., and Ballance, C.: Aneurysm of the Innominate Artery: A Twenty-Three Years' History, Lancet **1**:778 (April 14) 1934.

15. Greenough, J.: Operations on the Innominate Artery: Report of a Successful Ligation, Arch. Surg. **19**:1484 (Dec.) 1929.

radiated down his arm. For two years he suffered from this and by way of treatment took some pills, though what they contained he did not know; eventually however, the pain disappeared.

For the past nine years he had felt fairly well. Then about eight weeks before he entered the hospital, the pain in the shoulder returned. Along with it he noticed the appearance of a small nontender pulsating lump on the right side of his neck just above the clavicle. This grew rather rapidly at first but more slowly in the few weeks before his entry, finally attaining the size of an orange. He did not complain of any symptoms from compression, such as dysphagia or dyspnea; however, he did have a slight hacking cough.

For two weeks before entering the hospital he suffered from what he described as a boring pain between the shoulders. This was relieved when he sat up and also by strenuous exercise, such as chopping wood.

Fig. 1 (case 1).—Aneurysm of the innominate artery. The inner half of the right clavicle is obscured. The thyroid cartilage and the trachea are displaced to the left. The prominent bulging just below the thyroid cartilage was the site of greatest pulsation and later became the site of rupture.

On physical examination he was observed to be well developed and robust, presenting a large pulsating lobulated mass in the right side of his neck. It measured 8 cm. in diameter at the base and projected outward for a distance of 4 cm. Its outer lateral portion was firm, as compared to the inner portion near the midline, where it was thin walled. The right sternoclavicular joint was displaced anteriorly. The skin over the mass was bluish and purplish and was darker than the surrounding skin. The trachea was markedly displaced to the left, and the right sternomastoid muscle was pushed to the right by the tumor. Visible pulsation also was seen in the left lower portion of the back in the ninth and tenth intercostal spaces, where there was considerable retraction of the thoracic wall as well.

The heart sounds were heard in the mass, but there was no bruit. There was tenderness over the right sternoclavicular joint. The apex impulse of the heart was seen and felt within the midclavicular line. There was no increase in retrosternal dulness, nor was there increased dulness in the second or third right inter-

costal spaces. The sounds were regular and of good quality. A soft blowing systolic murmur was heard in the second right intercostal space, but no diastolic murmur was heard. The second aortic sound was not accentuated.

There was a slight amount of peripheral sclerosis. The blood pressure in the two arms was the same. The pulse volume was thought to be less in the right arm than it was in the left. The venous pressure was 80 mm. of water in the right arm and 95 mm. of water in the left. No rales were heard in the lungs, though on both sides of the upper portion of the chest the breath sounds were suppressed. The voice was normal, and there was no laryngeal paralysis. The right pupil was slightly larger than the left.

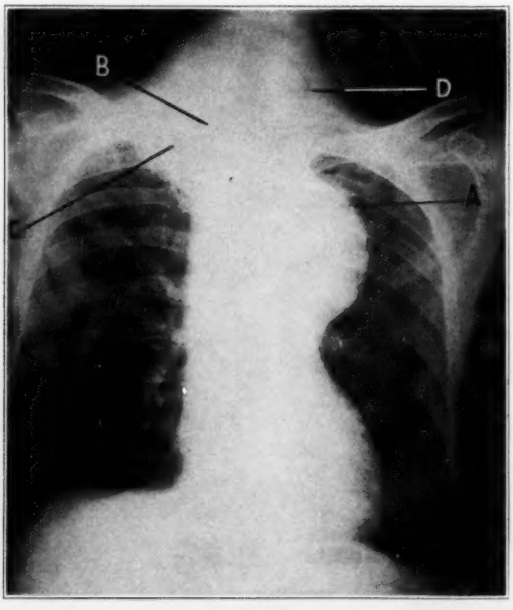


Fig. 2 (case 1).—Roentgenogram showing (*A*) the sacculated aneurysm of the descending portion of the aorta just beyond the arch, with calcified plaques in the wall of the sac seen in the third left intercostal space; (*B*) the aneurysm of the innominate artery; (*C*) erosion of the sternal end of the right clavicle, and (*D*) deviation of the trachea.

It is worth reemphasizing that there were no symptoms of compression, in spite of the fact that the trachea and the larynx were so markedly displaced.

The urine and blood were normal. The Wassermann reaction was positive. Numerous electrocardiographic tracings at times showed many extrasystoles of auricular and ventricular origin, though no other abnormality in rhythm was ever noted; the ventricular complex was abnormally slurred and notched, suggesting an impaired myocardial function.

Roentgenologic and fluoroscopic examinations of the chest revealed a dilated aortic arch with an aneurysm of the descending portion of the aorta and an aneurysm of the innominate artery. The heart was but slightly enlarged. There

were displacement of the trachea to the left, erosion of the upper border of the first rib, erosion and displacement of the sternal end of the right clavicle and erosion of the right borders of the second, third and fourth thoracic vertebrae.

By way of treatment the patient was put to bed. At first he complained bitterly of pain in the right shoulder joint and was given opiates for relief. On the third day of hospitalization his temperature became slightly elevated, there was leukocytosis and the pain was increased. This febrile episode lasted for four days; it was thought that he might have had a small rupture in one of the aneurysms. Antisyphilitic treatment was administered in the form of bismuth subsalicylate and potassium iodide and eventually small doses of neoarsphenamine. Under this therapy his condition definitely improved; he was able to sit up, shave himself and walk about without discomfort. During this period of observation, however, the tumor in his neck appeared to increase in size rather than to diminish.

He grew to feel so well that he was discharged in comparatively good condition after seventy-three days of hospitalization. A few days later, however, he walked a distance of approximately five miles, and shortly afterward there developed what he thought was a severe cold with a cough. The mass in his neck became painful, and the overlying skin became reddish. On one of the prominent lobulations near the midline there appeared a discolored area which looked like beginning ulceration. He became anxious over the changes which had taken place in the tumor and therefore returned to the hospital.

Fig. 3 (case 1).—Rupture of the aneurysm of the innominate artery. Osler said in regard to similar cases: "Reddening of the skin occurs with edema. A spot of necrosis forms which increases in size slowly. The aneurysm first 'weeps' and finally bursts with fatal hemorrhage." In this case the spot of necrosis grew to form an ulcer, 3 cm. in diameter, before the final rupture.

The physical findings were unchanged except that the mass in the neck pulsated more violently than before and the skin over it was cyanotic and edematous. It was a case of this type that Sir William Osler [1] must have had in mind when he described the events that take place in external perforation of an aneurysm: "Reddening of the skin then occurs with edema. A spot of necrosis forms which increases in size slowly. The aneurysm first 'weeps' and finally bursts with fatal hemorrhage." This is precisely what happened in the present case in the course of the next few days.

The necropsy confirmed the clinical findings. There were a large saccular aneurysm of the innominate artery with perforation, a fusiform dilatation of the arch of the aorta, resulting from old syphilitic aortitis, and an aneurysm of the

descending aorta which extended to the midthorax. The innominate aneurysm measured 10 cm. in length and 7.5 cm. in diameter. It was filled with soft, dark crimson clot. It had eroded through the sternal end of the right clavicle and the right borders of the second, third and fourth thoracic vertebrae, it had flattened the right lobe of the thyroid gland and it had displaced the trachea, without, however, obstructing either it or the esophagus. Death, of course, occurred from external rupture, with almost immediate exsanguination.

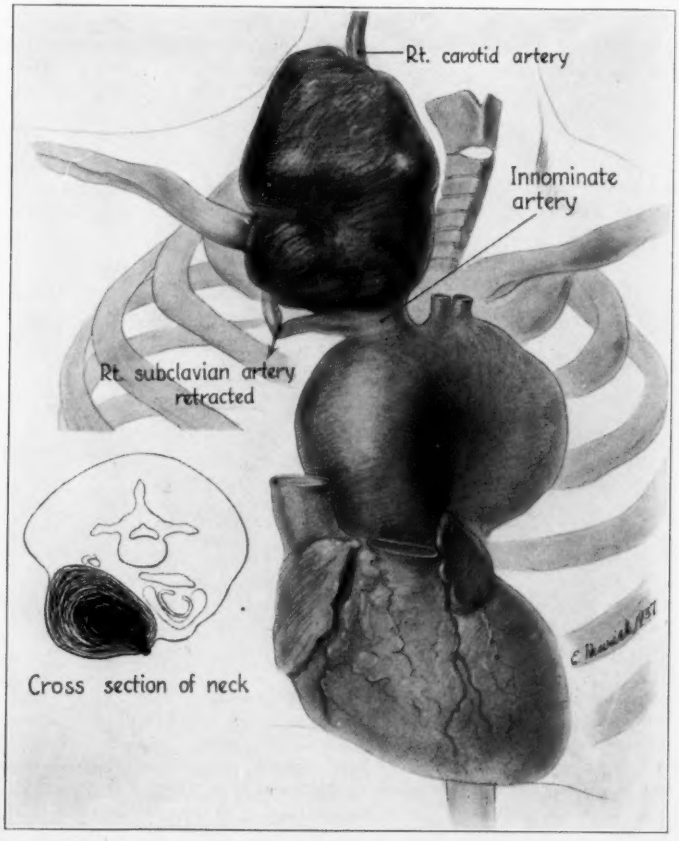


Fig. 4 (case 1).—Showing the relation of the aneurysms to the thoracic cage and the structures in the neck.

This was the first case of aneurysm that I had seen in which rupture occurred. It made an unforgettable impression, particularly as there still is uncertainty in my mind as to whether surgical treatment combined with antisyphilitic treatment was not indicated and might not have produced a more satisfactory therapeutic result than did medical treatment alone.

Obviously a great deal is known of innominate aneurysm. Its topographic anatomy has been abundantly described. Its symptoms also are well recognized. Usually the earliest symptom is pain in the right shoulder. A pulsating tumor in the neck soon is likely to appear. The tumor spreads along the line of least resistance, and this characteristically is upward under the sternomastoid muscle into the neck or, more rarely, downward into the mediastinum or pleural cavity, displacing the heart to the left. Curiously, although the aneurysm advances and erodes, compresses and displaces, it is less likely to cause symptoms from pressure on structures like the larynx and trachea than is an aneurysm arising in the aorta. This usually is regarded as an important differential point; an aneurysm of the arch of the aorta is notorious for giving early signs of compression because of the narrow space between the posterior surface of the sternum and the bodies of the vertebrae. An

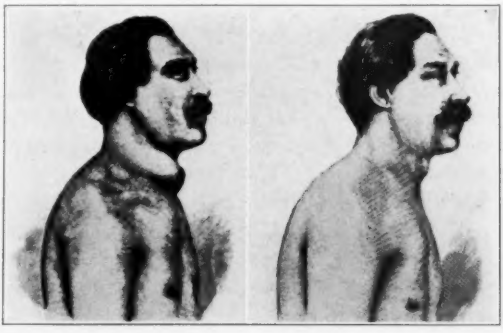

Fig. 5.—Figures from the case report by Richard Barwell (1877). The right common carotid and subclavian arteries were ligated. The patient lived a few months after operation and died of bronchopneumonia following exposure. Necropsy showed a small innominate aneurysm that was shrunken and sclerosed.

innominate aneurysm, in contrast, has more room in which to grow. If present in the neck, it is likely to be high, while an aneurysm of the arch will not extend much above the clavicular line. Finally, roentgenography and fluoroscopy should make it possible to recognize a thoracic aneurysm easily and to determine the point of origin with great accuracy.

That any internal aneurysm is essentially a hopeless affliction is certain. An innominate aneurysm, like any other aneurysm, is likely to rupture—not often externally but frequently into the trachea, bronchus, esophagus, mediastinum or pericardial or pleural cavity. Rupture is the common cause of death.

In recent years the medical treatment of thoracic aneurysm has received all the emphasis, the modern textbook of medicine failing to

emphasize the essential anatomic difference between aneurysm of the aorta and aneurysm of the vessels at the base of the neck and the fact that their therapy may differ. One must go back to Osler to be told that the differential diagnosis of aneurysm presenting in the neck is important because such an aneurysm is amenable to surgical procedures while one near the base of the heart is not.

No doubt the improving therapy of syphilis has much to do with modern indifference to aneurysms. In the first place, aneurysms now are comparatively rare and are likely to become even rarer as syphilis is recognized more easily and treated more adequately. In the second place, even the medical treatment of aneurysm is vastly better than it was, for example, when Osler wrote the first draft of his textbook. Now, as Moore, Danglade and Reisinger [16] have reported, prompt symptomatic relief, especially relief of paroxysmal and exertional dyspnea and of pain, is likely to be obtained in the medical treatment of aneurysm, and life is prolonged. Nevertheless, in spite of such advances in medical treatment, I believe that Osler's opinion should still be maintained. The differential diagnosis of aneurysm presenting in the neck still is important because such an aneurysm is amenable to surgical procedures while one near the base of the heart is not. If one could duplicate Barwell's [9] case, Schwyzer's [12] case (in which the patient lived for more than twenty-five years after ligation) or Miller's [14] case (in which the patient lived for twenty-three years after ligation), one would feel well satisfied.

As has been mentioned, the surgical procedures which have been advocated for the treatment of innominate aneurysm include ligation of the right common carotid artery and the right subclavian artery; ligation of the innominate artery and vein as well; wiring and the causation of clot formation by electricity within the aneurysmal sac, as suggested by Reid; [17] injection of quinine hydrochloride and ethyl carbamate, as suggested by Miller [14] for the same purpose, and even production of an arteriovenous fistula between the common carotid artery and the internal jugular vein, as suggested by Babcock [18] and McCarthy.[19]

16. Moore, J. E.; Danglade, J. H., and Reisinger, J. C.: Treatment of Cardiovascular Syphilis: Results Obtained in Fifty-Three Patients with Aortic Aneurysm and in One Hundred and Twelve with Aortic Regurgitation, Arch. Int. Med. **49**:879 (June) 1932.

17. Reid, R. M.: Aneurysms in the Johns Hopkins Hospital: All Cases Treated in the Surgical Service from the Opening of the Hospital to January 1922, Arch. Surg. **12**:62 (Jan.) 1926. Reid and Andrus.[2]

18. Babcock, W. W.: Newer Surgical Methods of Treating Diseases of the Vascular System, Am. J. Surg. **16**:401 (June) 1932.

19. McCarthy, P. A.: Treatment of Aneurysms of the Thoracic Aorta and Innominate Artery by Distal Arteriovenous Anastomosis: Observations of Ten Cases with Operations in Eight Cases, Ann. Surg. **91**:161 (Feb.) 1930.

No doubt technical difficulties in the way of these operations may be great. On the other hand, the skill of the modern surgeon is uncanny. In reconsidering the case which has just been described, it might have been possible, in the light of the necropsy observations, for a dextrous surgeon to have tied the subclavian and carotid arteries without rupturing the aneurysm, and this might have been a more beneficial form of treatment than the one employed. I believe that the same argument can be applied to the following case of a patient of Dr. Joseph Pratt and Dr. Samuel Proger at the Boston Dispensary, the record of which they have allowed me to study and to include in this paper:

Case 2.—A 48 year old Scotchman, a seedsman, was admitted to the diagnostic ward of the Boston Dispensary on July 25, 1932. He complained of a lump in

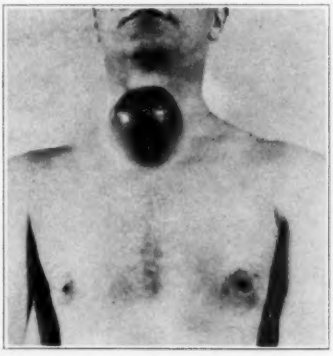

Fig. 6 (case 2).—A large innominate aneurysm presented at the base of the neck, with an area of necrosis in its most prominent part, at which point the final rupture took place. (Reproduced with the permission of Dr. Pratt and Dr. Proger, of the Boston Dispensary.)

his neck. When he was 18 he had a penile sore followed by a rash. This was untreated, though in 1927 he received six injections of arsphenamine for "recurring sore throat."

He had been well all his life until about two months before he entered the hospital. Then he noticed the appearance of a small tumor on the lower right side of his neck. This grew rapidly, it pulsated, it was not painful and it caused no symptoms of pressure.

Physical examination revealed just above and to the right of the suprasternal notch, an oval pulsating mass, 5 by 4 by 2.5 cm., over which the skin was tense and reddened. The sternomastoid muscle was displaced by the tumor. The retrosternal dulness was increased. The heart was not enlarged. No murmurs were heard. The lungs were normal. The blood and urine were normal. While the Wassermann reaction was negative, both the Kahn and the Hinton test gave a positive reaction. Roentgenologic and fluoroscopic examination of the chest showed a large expansile mass in the right upper portion of the mediastinum apparently

continuous with the ascending aorta but extending upward and forward in the neck. The tumor had eroded the manubrium and the sternal end of the right clavicle, and it had displaced the trachea slightly to the left. Five months later the tumor had increased greatly in size, and the skin over it was necrotic. Presently this area of necrosis increased slowly, the aneurysm began to weep and eventually it burst, with fatal hemorrhage.

While necropsy was not performed, a comparison of the findings in this case with the findings in the former case makes it seem highly

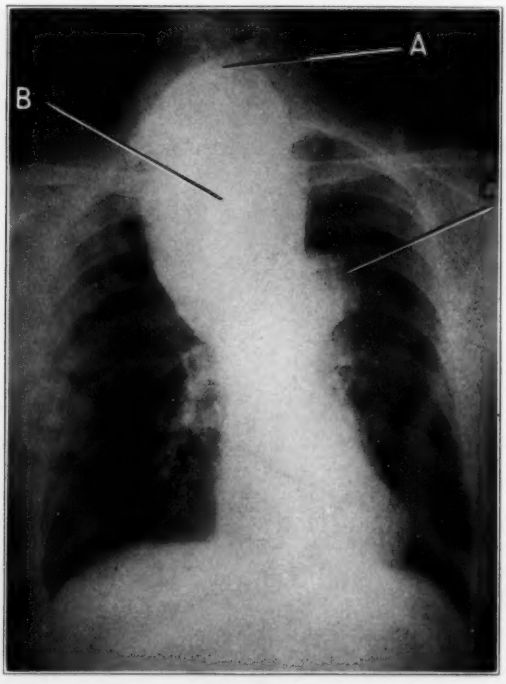


Fig. 7 (case 2).—Roentgenogram showing (*A*) the superior border of the aneurysm presenting in the neck; (*B*) the sacculated innominate aneurysm continuous with the ascending aorta and extending up into the neck and (*C*) the arch of the aorta displaced to the left. This was not an aneurysm of the aorta, as verified by fluoroscopy. The trachea cannot be seen in this roentgenogram on account of the density of the mass, but by fluoroscopy it was shown to be displaced to the left. (Reproduced with the permission of Dr. Pratt and Dr. Proger, of the Boston Dispensary.)

probable that here too was an innominate aneurysm with rupture. Probably it would scarcely have been feasible to tie the innominate artery in this case, but possibly ligation of the subclavian and carotid arteries might have been accomplished with good effect.

In certain cases technical difficulties brought up by the complicated anatomic relations of an innominate aneurysm may make the surgical treatment of the tumor almost impossible.

CASE 3.—An American painter 65 years old was admitted to the Massachusetts Memorial Hospitals on Dec. 13, 1930. He denied having had syphilis, though the Kahn and Hinton tests gave positive reactions. About ten years before entrance he first began to have palpitation of the heart and frequent spells of coughing. About a year before entry he was forced to give up work because, in addition to persistent dyspnea and orthopnea, he had edema of the legs.

There was no visible or palpable tumor of the neck. The heart was enlarged on percussion. No murmurs were heard. A roentgenogram of the chest showed a large dense shadow at the apex of the right lung and in the anterior mediastinum, due apparently to a mass, which appeared to displace the heart downward and to the left and which also displaced the trachea to the left. The patient died of congestive heart failure. Necropsy revealed an aortic aneurysm involving the innominate and right subclavian arteries as well as the arch of the aorta.

In this case, in which the innominate aneurysm had grown downward rather than upward, in which the aneurysm was practically inseparable from the arch of the aorta and in which it also involved the right subclavian artery, any successful operative procedure would have been almost unthinkable.

These 3 cases make a large enough group from which to draw certain generalizations concerning aneurysm of the innominate artery with which to awaken interest in an unusual medical disorder which has apparently been neglected of late by clinicians. Aneurysm of the innominate artery is rare, but its recognition is important. It differs from an aneurysm of the aorta by being more amenable to surgical treatment. An innominate aneurysm has a fairly definite clinical course and a clinical picture which make diagnosis possible in the majority of instances, especially when roentgenograms and fluoroscopy are available as diagnostic aids. The presence of a pulsating tumor above the episternal notch should make one suspicious of an aneurysm of the innominate artery which is presenting in the neck. The most satisfactory treatment of aneurysm of the aorta consists in the long-continued, intelligently administered treatment of syphilis. Treatment of aneurysm of the innominate artery not only should include treatment of the syphilis but also should be regarded as having surgical implications. The surgical attack should be undertaken early, before the aneurysm becomes large, as it should be borne in mind that the aneurysm may grow rapidly in the course of several weeks. It may be that the combination of antisyphilitic and of surgical treatment will accomplish in selected cases a more perfect therapeutic result for this type of aneurysm than has been hitherto generally obtained.

# DARK ADAPTATION OF THE EYE AND VITAMIN A STORAGE IN YOUNG ADULTS

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Evidence for the belief that night blindness represents the first symptom of vitamin A deficiency has been accumulating for some time.

Until recently the condition of night blindness has been considered rare in North America. Hess and Kirby,[1] seeking to determine the incidence of the condition, sent questionnaires to American ophthalmologists inquiring as to the number of cases that they had identified among their patients, and all who reported stated that night blindness is uncommon. This was interpreted to mean that deficiency of vitamin A is of infrequent occurrence in North America.

The later work of Jeans and Zentmire [2] with the Birch-Hirschfeld visual photometer and that of Jeans, Blanchard and Zentmire [3] with the biophotometer indicated that night blindness is common among children. These workers also presented evidence of vitamin A deficiency as a causative factor. Likewise the study of Park [4] and of Jeghers,[5]

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A preliminary report, an abstract of which appeared in the *Journal of Home Economics* for October 1937, was presented before the division on food and nutrition at the thirtieth annual meeting of the American Home Economics Association at Kansas City, Kan., on June 22, 1937.

1. Hess and Kirby, cited by Eddy, W. H., and Dalldorf, D.: The Avitaminoses, Baltimore, Williams & Wilkins Company, 1937.

2. Jeans, P. C., and Zentmire, Z.: A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, J. A. M. A. **102**:892-895 (March 24) 1934; The Prevalence of Vitamin A Deficiency Among Iowa School Children, ibid. **106**:996-997 (March 21) 1936.

3. Jeans, P. C.; Blanchard, E., and Zentmire, Z.: Dark Adaptation and Vitamin A.: A New Photometric Technic, J. A. M. A. **108**:451-458 (Feb. 6) 1937.

4. Park, I. O.: Preliminary Observations of Vitamin A Deficiency as Shown by Studies with the Visual Photometer, J. Oklahoma M. A. **28**:359-364 (Oct.) 1935.

5. Jeghers, H.: Night Blindness as a Criterion of Vitamin A Deficiency: Review of the Literature, with Preliminary Observations of the Degree and Prevalence of Vitamin A Deficiency Among Adults in Both Health and Disease, Ann. Int. Med. **10**:1304-1334 (March) 1937.

using the Birch-Hirschfeld photometer, pointed to the frequent occurrence of night blindness and of moderate vitamin A deficiency among adults.

The purpose of our study was (1) to obtain data to use in setting up standards for normal biophotometric readings for young women, (2) to determine the extent to which poor dark adaptation occurs in young college women and (3) to seek further evidence for the relation between vitamin A deficiency and subnormal dark adaptation, as measured with the biophotometer.

At the time that this study was made there were no reports of biophotometric tests on adults. There has since been published the work of Jeghers [6] with freshman medical students, chiefly men, employing this newer photometric technic. The author reported relatively poor dark adaptation in 35 per cent of the subjects tested.

## METHOD

The subjects for our study were freshman women ranging in age from 17 to 22 years. As a matter of convenience they were chosen from the students attending the freshman classes on foods at Purdue University, with no attempt at special selection.

Each subject was asked to keep a record of her diet for one week, with the thought that such a record might serve as an indication of the dietary habits of the subject and might possibly account for any marked individual variation in vitamin A storage. In order to secure as accurate and detailed a record as possible, each subject was asked to keep slips recording the number and size of servings (small, medium or large) of each food eaten. Between-meal "snacks" were also included. Daily summaries were made from these slips on special forms prepared for the purpose. From these forms weekly dietary summaries were made so as to permit comparison of the diets of the different subjects.

Approximately half the total group were living at the Women's Residence Hall, their period of residence having covered about four months. The other half secured meals from a variety of eating places on and off the campus.

The testing technic was essentially that of Jeans, Blanchard and Zentmire.[3] In order to insure the carrying out of all the tests in a uniform manner, detailed directions for each step of the procedure, including instructions to the subject, were formulated, and these directions were carefully followed.

Single tests were made for 94 students. Those showing relatively poor dark adaptation were tested again in a few days, and if confirmation of the first test was obtained, they were selected for further study. In a few instances a third test was made, with the result that there were some eliminations and a final selection of 16 subjects to serve as an experimental group. To this group were added 2 subjects whose biophotometric tests indicated good dark adaptation. The subjects were paired on the basis of the biophotometric readings, the readings in most instances showing little divergence for the members of a pair. One member of each pair served as a control and the other received, in addition to the regular

6. Jeghers, H.: The Degree and Prevalence of Vitamin A Deficiency in Adults, with a Note on Its Experimental Production in Human Beings, J. A. M. A. **109**:756-761 (Sept. 4) 1937.

diet, three halibut liver oil capsules daily, representing 28,000 to 29,000 U. S. P. units of vitamin A.[7] Tests were repeated at weekly intervals on the controls and on those receiving halibut liver oil, the members of a pair being tested on the same day of each week. The experiment was continued for five weeks.

## RESULTS

An arbitrary grouping of the initial readings for recovery after exposure to the bright light for the original 94 biophotometric tests and the distribution of the subjects over the range of readings obtained are recorded in table 1.

An appraisal of the results in terms of normal is difficult to make as work with the biophotometer, particularly with adult subjects, is too limited as yet to furnish anything definite in the way of standards. In this study the subjects having a light requirement greater than 1.5 milli-foot-candles immediately after exposure to the bright light were definitely considered to have poor dark adaptation. It was from this group that 16 of the experimental subjects were chosen. Second and

TABLE 1.—*Results of Biophotometric Tests*

| Initial Recovery Reading, Milli-Foot-Candles of Light | Number of Subjects | Per Cent of Total |
|---|---|---|
| Less than 0.5 | 10 | 10.6 |
| 0.5 to 1 | 33 | 35.1 |
| 1 to 1.5 | 26 | 27.7 |
| Greater than 1.5 | 25 | 26.6 |

third tests, however, gave readings that placed some of them in the group immediately above, with the readings for 3 of the subjects falling slightly below the lower range for that group. The 2 experimental subjects representing good dark adaptation were selected from the first two groups, with readings of 0.38 and 0.52 milli-foot-candle, respectively.

Attention is centered on the first reading of the recovery period after exposure to the bright light, because it appears to be the most significant one. Jeans, Blanchard and Zentmire, however, while emphasizing the importance of this reading have regarded the entire period of recovery as having significance. They have stated that those with normal dark adaptation have final readings of less than 0.05 milli-foot-candle except in cases in which the "visual threshold" is increased by causes other than vitamin A deficiency. In the present study 3 of the 5 subjects whose final readings were 0.05 milli-foot-candle or greater were in the group showing the most deficiency (initial readings for the period of recovery greater than 1.5 milli-foot-candles). One was in the group with readings of 1 to 1.5 milli-foot-candles, and the other showed readings close to the upper limit of the range 0.5 to 1 milli-foot-candle.

7. The capsules, with assay figures, were supplied through the Wm. S. Merrell Co., Cincinnati.

The results of the analysis of the dietary records are shown in table 2. An examination of this table reveals nothing that would account for marked variations in the vitamin A intake of the subjects, so that the differences in vitamin A storage which the biophotometric readings seem to indicate cannot be explained on the basis of the eating habits of the subjects at the time that the tests were made. A question might be raised, however, as to how far such records may be relied on to give a true picture of even the qualitative aspects of the diet.

TABLE 2.—*Analysis of the Dietary Records, Showing the Average Servings per Person per Day*

| Group* | Vegetables | | | | | Fruits | | | | Cereals Other Than Bread | Meat, Fish, Poultry | Eggs, Cheese | Coffee, Cocoa, Cola, Malted Milk | Cake, Pastry, Sweets |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Milk | Green | Yellow | Potatoes | Other | Oranges | Grapefruit | Tomatoes | Other | Bread | | | | |
| A | 1.31 | 0.93 | 0.29 | 0.77 | 0.53 | 0.22 | 0.30 | 0.27 | 1.55 | 2.90 | 0.37 | 1.42 | 0.51 | 1.72 | 1.34 |
| B | 1.04 | 1.00 | 0.26 | 0.76 | 0.50 | 0.18 | 0.28 | 0.28 | 1.83 | 2.80 | 0.24 | 1.45 | 0.40 | 1.07 | 1.45 |
| C | 1.34 | 0.98 | 0.28 | 0.62 | 0.76 | 0.16 | 0.51 | 0.35 | 1.80 | 2.98 | 0.17 | 1.48 | 0.52 | 0.84 | 1.12 |

* Group A represents the total group, group B includes 16 subjects with good dark adaptation and group C includes 16 subjects with poor dark adaption. Two subjects in group B had been taking cod liver oil or vitamin A concentrates.

TABLE 3.—*Initial Recovery Readings in Milli-foot-Candles*

| Subjects Receiving Halibut Liver Oil | | | | | | | Controls | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject No. | Original Test | Week of Experiment | | | | | Subject No. | Original Test | Week of Experiment | | | | |
| | | 1st | 2nd | 3rd | 4th | 5th | | | 1st | 2nd | 3rd | 4th | 5th |
| 7 | 0.72 | 0.76 | 0.58 | 0.29 | 0.58 | 0.38 | 81 | 0.63 | 0.69 | 1.00 | 0.84 | 0.92 | 0.84 |
| 11 | 1.95 | 1.48 | 1.00 | 0.44 | 0.84 | 0.76 | 73 | 1.95 | 1.80 | 1.48 | 1.60 | 1.80 | 1.80 |
| 84 | 1.48 | 0.63 | 0.76 | 0.76 | 1.00 | 1.10 | 2 | 1.48 | 1.36 | 1.36 | 1.36 | 1.80 | 1.80 |
| 52 | 1.36 | 1.00 | 0.315 | 0.69 | 0.52 | 0.44 | 70 | 1.22 | 1.10 | 0.63 | 0.76 | 0.69 | 0.63 |
| 27 | 1.48 | 1.00 | 0.52 | 0.58 | 0.69 | 0.69 | 76 | 1.22 | 1.36 | 1.00 | 1.22 | 1.00 | 1.36 |
| 32 | 1.22 | 1.36 | 0.36 | 1.10 | 1.00 | 1.00 | 36 | 0.92 | 1.48 | 1.22 | 0.92 | 1.36 | 1.10 |
| 60 | 1.95 | 1.36 | 1.00 | 1.36 | 0.63 | 0.84 | 71 | 1.00 | 0.84 | 1.22 | 1.60 | 1.80 | 1.10 |
| 88 | 2.16 | 1.95 | 1.36 | 1.48 | 0.76 | 0.92 | 46 | 1.48 | 1.80 | 2.40 | 0.69 | 2.40 | 1.36 |
| 90* | 0.52 | 0.24 | 0.29 | 0.18 | 0.16 | 0.195 | 59* | 0.38 | 0.44 | 0.47 | 0.63 | 0.63 | 0.69 |

* Subjects 59 and 90 are the two whose original readings placed them in the group considered to have good dark adaptation.

In table 3 are recorded the weekly initial readings made during recovery for the subjects receiving halibut liver oil and for their respective controls over a period of five weeks. It will be noted that there were fluctuations back and forth in both groups, but definite improvement in the subjects to whom the halibut liver oil capsules were administered was evidenced by the decreased requirements of light of the latter after the first or second week in contrast to that of the controls, for whom subsequent readings were in most cases as high as or higher than those obtained at the beginning. The improvement in the subjects who originally showed a high requirement of light is in accord with the findings of other workers. But the results obtained with the pair con-

sidered to have good dark adaptation seem to point to something that has not previously been noted, that is, the possibility that even very low readings may not indicate optimal storage of vitamin A. This point is now under further investigation.

There was rather wide variation in the minimal biophotometric readings obtained for the different subjects receiving halibut liver oil. The time required to reach this stage also varied, the range being from one to four weeks, with no consistent relation between the original readings and the time period. There were few instances in which there was improvement after four weeks.

These observations seem to suggest that there are individual variations with regard to what constitutes the best dark adaptation obtainable. It also appears that the intake of vitamin A necessary for optimal storage varies with different subjects, assuming that optimal storage for a given subject has been obtained when no further improvement results with a continued high intake of vitamin A. A better interpretation of the results observed may be that they indicate a varying ability to utilize and store the ingested vitamin A, particularly as it affects the rate of regeneration of the visual purple.

## SUMMARY AND CONCLUSIONS

Single biophotometric tests of a group of 94 college freshman women gave readings that were interpreted to indicate poor dark adaptation in at least 26.6 per cent of the cases.

The daily administration of 28,000 to 29,000 U. S. P. units of vitamin A in the form of halibut liver oil capsules to half the 18 experimental subjects resulted in lowered readings in contrast to those for the respective controls, which were in most instances as high as or higher at the end of the five week experimental period than at the beginning. This improvement in the subjects receiving halibut liver oil and the failure of the corresponding controls to improve was evident not only in the eight pairs of subjects whose original tests were thought to indicate poor dark adaptation but also in the pair who at the beginning of the experiment appeared to have good dark adaptation. The improvement, however, did not always proceed regularly; there was some fluctuation back and forth both for the subjects receiving halibut liver oil and for the controls.

Minimal biophotometric readings, as well as the time required to reach this stage, varied with the different subjects to whom the halibut liver oil was administered.

The pair with good dark adaptation gave lower original readings than were ever attained by most of the more deficient subjects, yet the member of this pair to whom halibut liver oil was administered proved to be capable of further improvement.

The improvement resulting from the administration of halibut liver oil to the more deficient subjects agrees with the findings of other workers and gives increased evidence for the alleged relation between vitamin A deficiency and subnormal dark adaptation, as measured with the biophotometer.

The study also furnishes meager evidence for the view that even low readings may not indicate optimal vitamin A storage. There is need for further investigation on this point.

In general, it may be concluded that there is a variation in what constitutes the best dark adaptation obtainable for a given person. It appears that there are differences in the ability to utilize and store the vitamin A ingested beyond a certain point, particularly as it affects the rate of regeneration of the visual purple in adapting the eye to dim illumination.

# BILATERAL SPOROTRICHOSIS OF THE BREAST

## REPORT OF A CASE

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A careful though not complete survey of the literature covering sporotrichosis fails to reveal any reports of cases of invasion of the female breast by Sporothrix. We are recording the present case because of its unusual diagnostic features and because of the complete laboratory confirmation of the tentative diagnosis. It is of note that the prompt therapeutic response likewise authenticated the diagnostic premise.

The first recorded instance of sporothrix infection occurred in 1896.[1] The organism in this case was identified by Irwin F. Smith and was named Sporotrichum schenckii in honor of the clinician who first recognized the etiologic factor responsible for the ulcerated lesion on the forearm of the patient. Since the identification of this parasitic fungus, several other cases have been recognized, notably a series of 10 cases reported by Foerster in 1926.[2]

Sporotrichosis is a chronic infection of the cutaneous and internal structures due to various forms of the spore-forming filamentous fungi of the Sporothrix group. The cases in human beings recorded in the literature concern primarily the cutaneous form of the disease, in which the subcutaneous tissues are affected and in which only rarely is there dissemination to deeper or visceral organs. Various clinical forms are described, as follows:

1. A disseminated gummatous form, in which firm nodular swellings appear which ultimately form small abscesses with ulceration and with the production of a chronic persistent discharge
2. The ulcerative type, which appears to be common on the hands and arms and which strongly resembles the cutaneous form of tuberculosis
3. The so-called extracutaneous forms, in which ulcerous areas are found in the mucous membranes, glands, lungs, periosteum, bone or muscle
4. An internal form, which is presumably secondary to some cutaneous form but which has the characteristics of an acute febrile illness

1. Osler, W.: Principles and Practice of Medicine, ed. 11, revised by Thomas McCrae, New York, D. Appleton and Company, 1930, p. 235.

2. Foerster, H. R.: Sporotrichosis: An Occupational Dermatosis, J. A. M. A. **87**:1605 (Nov. 13) 1926.

By far the most common type is the cutaneous or localized form, with secondary regional lymphangitis. The lesion may be said to be a primary sore at the site of inoculation; then in the course of a few days to several months, small painless indolent granulomas form, which may ulcerate and produce abscesses of the "cold" type. Secondary to ulceration there is the production of fistulas or sinus tracts. As a general rule the health of the patient is relatively unaffected, except in cases of the febrile internal type. Mild anemia is said to accompany the usual course of chronicity, which varies from one to three years.

Infection with the sporothrix is most common among farmers, gardeners and laborers. It has been called an occupational disease by Foerster,[2] who described 10 cases due to trivial wounds of the hands or arms from the thorns of barberry bushes. In the majority of reported cases a predilection for the hands, arms and lower extremities is noted, bearing out Foerster's contention. In our case it is interesting to note that the patient was probably exposed to infection while on a visit to a farm.

REPORT OF CASE

Mrs. C. M., 20 years of age, a resident in the city, presented herself to one of us (J. L. W.) with the chief complaint of "trouble with the breast." She stated that one and one-half years previously she was kicked in the left breast by an infant with whom she was playing. The trauma was trivial, and she forgot about it until about four months later, when she noted a small lump in the breast at the site of the bruise. Questioning revealed that she had been bruised while on a visit to the home of her parents in the country, where she was in the hay fields and in the garden a great deal. After the lump was noted the skin became reddened and within a few days apparently opened spontaneously, with the discharge of greenish pus which had a foul odor and was streaked with blood. A chronic discharge was then noted for several weeks, and with the use of various "home remedies" the wound apparently closed. However, within a short time several other indurated areas appeared in the breast, which were incised by a physician, and drainage continued. Approximately ten months before she was seen by one of us (J. L. W.), while there was still a draining sinus in the left breast, a lump was noted in the upper outer quadrant of the right breast. This broke and followed about the same chronic course as that of the lump in the left breast. She stated that there had not been a great deal of soreness at any time, but she noted that the glands in both axillas were enlarged, although drainage had not appeared from those areas. Recently there had been some discharge of blood-streaked pus from the right nipple.

The family history was noncontributory, as was the patient's past medical history, in that there had been no serious illnesses. The marital history revealed that the patient suspected that she was approximately five months pregnant. There had been some milky discharge from both nipples. A systemic review revealed nothing of note other than a slight cough attributed to a "cold" during the past three weeks. There had been no previous pulmonary, cardiac or gastrointestinal symptoms.

Physical examination revealed a well nourished and well developed woman with a normal temperature, pulse rate and respiration. The blood pressure was 118 systolic and 76 diastolic. Examination of the head, eyes, ears, nose and throat

showed nothing remarkable. The thyroid gland was not enlarged, and there were no palpable cervical glands. Examination of the lungs and heart revealed no physical signs of a pathologic condition.

The appearance of the breast is shown in figure 1 *A*. Both breasts were enlarged, the areolas were pigmented and Montgomery's glands were prominent. In the left breast (fig. 1 *B*) there was a small sinus with indurated edges above and internal to the nipple. There were two healed sinuses, one in the internal upper quadrant and the other in the lower outer portion of the areola. In the most dependent portion of the left breast there was a large area of scar tissue in a sunburst arrangement. The breast had a hard, "ropy" feeling, and the axillary glands were palpable but nontender. In the right breast internal to the nipple was an open granulomatous-edged area, approximately the size of a quarter (fig. 1 *C*). From this, thick yellowish green pus exuded, and on pressure there were some bloody streaks. On palpation the condition of the breast was essentially the same

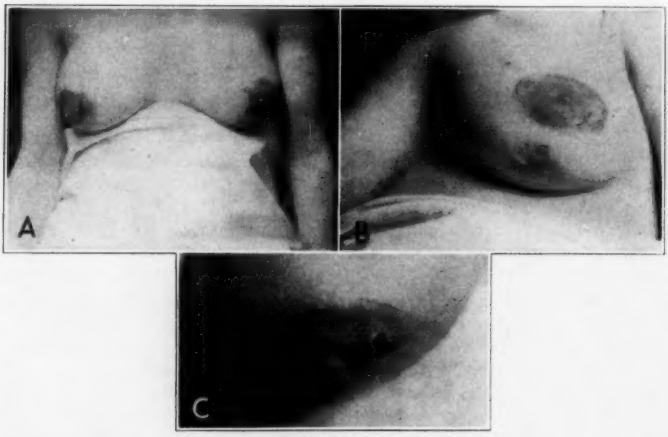


Fig. 1.—*A*, the appearance of the breasts before therapy was instituted. *B*, note the "sunburst" scar at the inferior pole. To the medial side of the upper inner portion of the nipple is an open fistula with a small headed sinus mesial and superior to it. *C*, the open granulomatous lesion on the medial side of the nipple of the right breast.

as that noted in the left side; the axillary glands were likewise enlarged. A little colostrum was expressed from both nipples.

Examination of the abdomen revealed no abnormal masses, the uterus was enlarged, there was no adenopathy and the spleen was not palpable. Pelvic examination confirmed the diagnosis of pregnancy of approximately five months. Rectal examination revealed nothing remarkable. Examination of the extremities showed no clubbing, cyanosis or edema. The neurologic examination likewise showed no abnormality.

In the office a smear was made of material from the lesion in the right breast and was examined under the microscope. At this first examination the presence of rather large, ovoid, clear bodies was detected. There were no myceliums, sulfur granules or other signs of fungoid organisms. After this examination a complete

bacteriologic and laboratory examination was made by one of us (A. R. K. M.). The bacteriologic investigation consisted of microscopic and cultural studies of the purulent discharge and of tissue from the margin of the ulcer of the right breast.

Smears of the pus were stained with the Gram, Wright and Löffler methylene blue stains. In each instance the smears showed abundant pus cells with a good

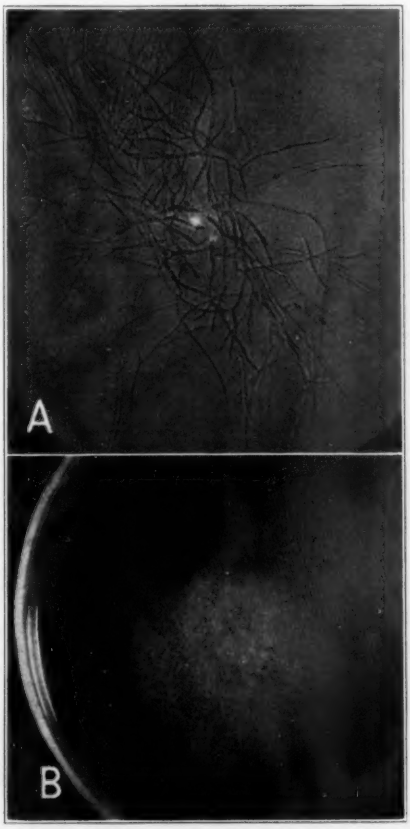


Fig. 2.—*A*, the mycelial growth in the original broth culture; × 440. *B*, subculture from the broth on Sabouraud's agar.

many large mononuclear endothelioid phagocytic cells. A few deeply staining, well defined oval bodies, 1 to 2 microns in diameter, were seen, and occasionally these occurred within the large mononuclear cells. No mycelial filaments could be demonstrated in these smears.

Cultures of the pus were made in nutrient dextrose broth, on blood agar and on Sabouraud's agar. None of the cultures on blood agar produced a growth.

Primary cultures on Sabouraud's agar were unsatisfactory for study owing to early contamination by the penicillium and the aspergillus.

Broth culture was made by plunging a cotton swab loaded with pus into the broth and leaving it in the medium continuously. After four weeks of incu-

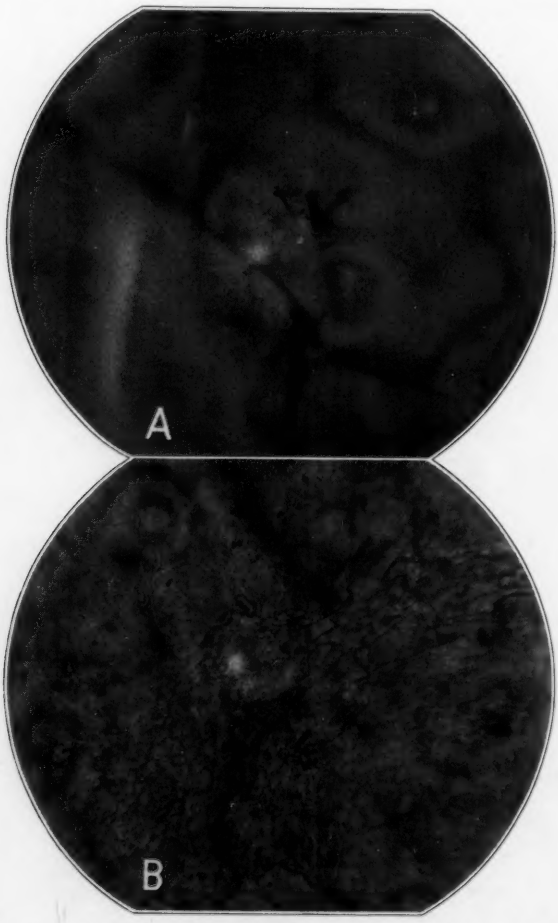


Fig. 3.—*A*, hyphae with terminal conidia from the colony shown in figure 2 *B*; × 440. *B*, mycelium deep in the cutaneous tissue at the margin of the ulcer; × 440.

bation at room temperature a fine, fluffy white growth was seen about the cotton swab. This subsequently extended up to the surface of the medium, where it formed a thick, filmy white coat. Microscopic study of this growth showed a

fine, branching, septate mycelium with no sporulating asci. Some short, thickened, irregular segments were noted along various hyphae (fig. 2*A*).

This organism was transferred to Sabouraud's agar and was incubated at 37 C. It grew rapidly, producing a large, filmy white colony, which later became faintly pinkish in its central part (fig. 2*B*). Microscopically this growth showed the same fine, branching, septate mycelium. There were no asci, and conidia were seen at the ends and on the sides of the hyphae, with some tendency to grouping in whorls (fig. 3*A*).

The tissue obtained was teased out, mounted in 10 per cent solution of potassium hydroxide and examined microscopically. Granulating tissue from the base of the ulcer revealed nothing pertinent, but the deeper layers of skin at the margin of the ulcer showed fine filaments of mycelium occurring in fairly dense clusters (fig. 3*B*). No definite septations in the hyphae could be made out, but several mounts showed similar structures, and remounting in saline solution and distilled water left these structures intact. They were considered to be of fungous origin and were definitely not artefacts.

On the basis of the bacteriologic observations (the positive results of culture and the presence of mycelium in the tissue), it was apparent that we were dealing with a mycotic infection. The character of the growth obtained placed the organism in the group of fungi imperfecti, or hyphomycetes, various members of which are common causes of dermatomycoses, notably the ringworm fungi, the malassezia and the sporothrix. The arrangement of the conidia at the sides and at the ends of the hyphae is typical of the structure considered to be characteristic of Sporothrix, and a diagnosis of sporotrichosis was therefore deemed to be justified.

The serologic investigation consisted of Wassermann and Kahn tests of the blood. These gave negative reactions.

## COMMENT

This case was interesting because of the chronicity of the condition and the apparent difficulty of making a diagnosis. Incision and drainage, presumably for abscesses, had been done on two occasions, with uniformly poor results. The general health of the patient had been unaffected. The complication of a five month pregnancy made it imperative to establish a definite diagnosis quickly in order to prepare the breasts for parturition.

*Differential Diagnosis.*—In the differential diagnosis we considered tuberculosis, syphilis, actinomycosis, blastomycosis, aspergillosis, other rarer types of fungous or yeast infection and lastly a streptococcic or staphylococcic infection. Tuberculosis was excluded by the normal roentgenographic appearance of the chest and the absence of other clinical signs of tuberculosis of the skin. The primary lesion of syphilis was excluded by the dark field and serologic studies. The tertiary gummatous form of syphilis likewise was excluded by the negative reactions to the Wassermann and Kahn tests and by the absence of other stigmas of either congenital or acquired syphilis. The exclusion of the various fungi and yeasts was a laboratory problem, and in this case we both found the causative organism in smears and at biopsy and were able to culture it. Streptococcic and staphylococcic infection

were ruled out by laboratory methods. Finally, as an aid in the differential diagnosis, the response to iodides was rather spectacular in this type of infection, although in certain cases of blastomycosis, therapeutic response to iodide medication is rather marked.

*Clinical Course and Treatment.*—After the diagnosis had been definitely established, oral therapy was begun with the use of potassium iodide, starting with 0.3 cc. three times a day and increasing to 2.5 cc. three times a day. At first, potassium iodide [3] in 1 Gm. strength was administered intravenously every third day. Local application of a weak tincture of iodine was employed on the open lesion. By the end of the second week the patient had not exhibited any sign of overdosage of iodide (in these cases the patients seem to tolerate iodides exceptionally well), and the lesion in the right breast had almost completely healed. At seven months the patient was delivered of a normal healthy infant. The breasts were completely healed, but it was thought wise to give the infant a formula immediately, as further iodide therapy was necessary to prevent recurrence of symptoms in the patient. It is wise in these cases to continue treatment for at least two months after all open lesions are apparently healed.

## SUMMARY

A case of bilateral invasion of the female breast by Sporothrix is recorded, with full laboratory confirmation and an excellent therapeutic response to iodide medication.

3. Shelmire, B.: Intravenous Iodine Therapy: Preliminary Report, Texas State J. Med. **22**:644 (Feb.) 1927.

# Progress in Internal Medicine

## BLOOD

A REVIEW OF THE RECENT LITERATURE

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The scope of a review of this nature is difficult to define precisely. So far as possible the object has been to include for consideration all articles which contribute new information to the subject of diseases of the blood and blood-forming organs, those which advance well thought-out speculations to explain observed phenomena and those which supplement or confirm the present beliefs. In the interests of the reader it has seemed best to correlate in connected exposition the material reviewed, although in accomplishing this it has at times been necessary to give what may seem undue weight to certain articles, while slighting others of equal merit. It is, of course, unavoidable that a number of significant communications should be passed over entirely, but it is hoped that such omissions may be corrected in succeeding reviews.

### PERNICIOUS ANEMIA

*General Considerations.*—It is generally accepted that achlorhydria is a constant feature of pernicious anemia and that the intrinsic factor of Castle is present in decreased amounts.[1] Kahn[2] studied the case records of 840 persons with pernicious anemia. None of the patients secreted hydrochloric acid, and in none was there evidence of peptic ulcer.

The original work of Castle and his co-workers, in which they demonstrated that a specific antianemic substance, the "intrinsic factor,"

From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.

1. Morrison, T. H.: The Role of the Gastric Secretion in Pernicious Anemia, Internat. Clin. **2**:131, 1937.

2. Kahn, J. R.: Absence of Peptic Ulcer in Pernicious Anemia, Am. J. M. Sc. **194**:463, 1937.

is produced in the wall of the stomach and is present in gastric juice but not in saliva or in the duodenal contents, indicated that the stomach alone of the gastrointestinal tract is the site of formation of the intrinsic factor. On strong theoretic grounds Thompson [3] questioned this assumption and reported a number of cases of pernicious anemia and nontropical sprue in which treatment with desiccated duodenal mucosa of swine was successful. It is recognized that these observations cannot be construed as direct proof of the presence of the antianemic substance in human duodenal mucosa. Further studies on this point are indicated. Tempka [4] fed 20 liters of saliva to a patient with pernicious anemia in relapse and observed reticulocyte response on the sixth day of treatment as well as symptomatic improvement. When the administration of saliva was discontinued, relapse occurred. The author stated the opinion that the hematologic changes were not the result of a spontaneous remission.

That interaction of the intrinsic and extrinsic factors is required for the normal maturation of red blood cells, although doubted by some, has never been disproved. Whether or not the intrinsic factor is present in the gastric juice of patients with pernicious anemia appears to be debatable. Fitz-Hugh and Creskoff [5] stated the opinion that the substance is absent, but after a consideration of their data, their conclusions do not appear warranted. It appears more likely that the deficiency of the intrinsic factor is quantitative rather than qualitative. Fouts, Helmer and Zerfas [6] showed that patients with pernicious anemia have a decrease of gastric secretion that is directly proportional to the level of the red blood cell count. They also concluded that the amount of fasting gastric content is dependent on the age of the patient, the presence and severity of changes in the central nervous system and the amount and type of antecedent therapy. Their observations were similar to those of Goldhamer [7] but are open to a different interpretation. Goldhamer stated that the gastric secretion in relapse is dependent primarily on the severity of the disease process and less on the age of the subjects, whereas in remission the gastric volume appears to be

3. Thompson, J. C.: Hematopoietic Response Following Oral Administration of Desiccated Duodenal Mucosa, Ann. Int. Med. **11**:39, 1937.

4. Tempka, T.: Die Bedeutung der Speicheldrüsen für die Pathogenese der Biermerschen Krankheit, Folia haemat. **57**:30, 1937.

5. Fitz-Hugh, T., Jr., and Creskoff, A. J.: Experiments with "Depepsinized" Human Gastric Juice in Treatment of Pernicious Anemia, Am. J. M. Sc. **192**:168, 1936.

6. Fouts, P. J.; Helmer, O. M., and Zerfas, L. G.: Gastrointestinal Studies: Volume of Gastric Juice in Pernicious Anemia, Am. J. Digest. Dis. & Nutrition **3**:904, 1937.

7. Goldhamer, S. M.: The Gastric Juice in Patients with Pernicious Anemia in Induced Remission, Am. J. M. Sc. **193**:23, 1937.

correlated with age. In addition to the volumetric studies it was shown that the combined juice of patients in relapse contained the intrinsic factor.

Several interesting experiments have been performed in an effort to determine the nature of the intrinsic factor. Helmer and Emerson,[8] in studying the interaction between the intrinsic and the extrinsic factor on incubation with liver extract and normal gastric juice, noted only a slight proteolytic effect, which they attributed to be due to peptic activity. Taylor and his co-workers [9] observed some alterations in casein metabolism with normal gastric juice at a $p_H$ of 7.4 and concluded that the changes were due to activity of the intrinsic factor. They did not imply that casein was the extrinsic factor. Helmer and Fouts [10] demonstrated that the intrinsic factor in gastric juice could be precipitated with saturated ammonium sulfate and that it was nondialyzable and was insoluble in 80 per cent alcohol.

Hernberg [11] demonstrated the presence of the intrinsic factor in the gastric contents of patients with anemia due to Bothriocephalus. Stasney and Higgins [12] injected concentrated gastric juice into pregnant rats. From observations of the number and the structure of the fetal erythrocytes before and after administration of gastric juice to the mothers, they concluded that they could detect the presence of the substance causing the development of the red blood cells. Mark and Hauke [13] also used the rat for the determination of the intrinsic factor in gastric juice. It was their conclusion that if reticulocytosis is obtained in this animal after the parenteral administration of gastric juice, the person from whom the gastric juice is obtained does not have pernicious anemia. If no reticulocyte response is observed, the patient may or

8. Helmer, O. M., and Emerson, C. P.: Studies on the Chemical Nature of the Interaction Between the Intrinsic and Extrinsic Antianemic Factors upon Incubation of Liver Extract and Normal Gastric Juice, Am. J. Digest. Dis. & Nutrition **3**:906, 1937.

9. Taylor, H. L.; Castle, W. B.; Heinle, R. W., and Adams, M. A.: Correlation of in Vitro Activity of Normal Human Gastric Juice on Casein at $p_H$ 7.4 with Gastric Intrinsic Factor, Proc. Soc. Exper. Biol. & Med. **36**:566, 1937.

10. Helmer, O. M., and Fouts, P. J.: Fractionation Studies on Intrinsic Factor in Normal Human Gastric Juice, Am. J. M. Sc. **194**:399, 1937.

11. Hernberg, C. A.: Concerning the Anti-Anaemic Influence of the Gastric Juice in Pernicious Bothriocephalus Anaemia, Acta med. Scandinav., 1936, supp. 78, p. 582.

12. Stasney, J., and Higgins, G. M.: The Effect of Normal Human Gastric Juice Administered to the Mother on the Size and Volume of the Erythrocytes of the Fetus, Proc. Staff. Meet., Mayo Clin. **12**:490, 1937.

13. Mark, R. E., and Hauke, G.: Ueber den Nachweis des Castleschen Fermentes im Magensaft bei Anämien, Ztschr. f. klin. Med. **132**:705, 1937.

may not have pernicious anemia. Wills, Clutterbuck and Evans [14] studied the macrocytic anemias of monkeys and concluded that both the intrinsic and the extrinsic factor are necessary for normal erythrogenesis.

The extrinsic factor of Castle has been found in a number of protein-containing foods, such as beef muscle, autolyzed yeast, wheat germ and egg white. On the other hand, casein has been reported by Castle and Townsend as giving a negative reaction with the intrinsic substance when incubated with gastric juice at a $p_H$ of 2.5 to 3.5. Miller and Pritchard [15] argued that since infants may be maintained on milk alone for long periods without developing pernicious anemia, it might be assumed that caseinogen, the chief protein of milk, probably contains the extrinsic factor. To test this hypothesis they treated with whole milk and gastric juice 2 patients with pernicious anemia, while maintaining them on a diet devoid of known sources of extrinsic factor. Fair hematologic responses were obtained in both cases, indicating the presence of extrinsic factor in the milk. Three other patients failed to respond to a mixture of gastric juice and whey, thereby suggesting that the extrinsic factor of milk is contained within the casein portion. However, insufficient amounts of whey may have been used in the mixture tested.

An attempt was made by Ungley [16] to secure a more potent liver fraction by supplementing the purification method of Dakin and West. A product prepared according to the method of Dakin and West (anahaemin) was first dissolved in phenol; anhydrous methyl alcohol was then slowly added so as to effect fractional precipitation. The first fraction was eliminated and the latter one retained. The resulting product was a light buff and contained 14.3 per cent nitrogen. Twenty patients with pernicious anemia were given this material to determine the minimum effective dose, and in 5 cases the double reticulocyte response was employed to compare its strength with that of the original preparation. It was found that a dose of 50 to 75 mg. gave results comparable to those obtained from 200 mg. of the original product. After the use of the double reticulocyte method, Ungley concluded that the potency of 2 mg. of the more purified fraction was greater than that of 5 mg. of the original preparation.

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14. Wills, L.; Clutterbuck, P. W., and Evans, B. D. F.: A New Factor in the Production and Cure of Certain Macrocytic Anaemias, Lancet **1**:311, 1937.

15. Miller, F. R., and Pritchard, W. H.: Presence in Milk of the Extrinsic Factor of Castle, Proc. Soc. Exper. Biol. & Med. **37**:149, 1937.

16. Ungley, C. C.: Further Purification of Dakin and West's Liver Fraction: Purified Anahaemin Compared with Original Product in Regard to Effect in Pernicious Anemia, Lancet **2**:1513, 1936.

Jacobson and Subbarow [17] suggested that the therapeutic activity of liver extract may depend on the presence of a number of chemically distinct substances. They said they believed that several accessory factors augment the activity of the primary factor. Of the three known accessory factors, one is l-tyrosine, another contains a complex purine and the third is a peptide. The chemical nature of the primary factor is undetermined. Without the activity of the primary factor the accessory factors are therapeutically inert, whereas the primary factor alone is only slightly active. The materials tested were given intramuscularly to patients with pernicious anemia in relapse, and evidence in support of the authors' hypothesis was derived in part from data concerning the production of reticulocytes but principally from observations of regeneration of erythrocytes.

Although the chemical identity of the essential substance in preparations therapeutically active against pernicious anemia is not known, Jacobs [18] attempted to synthesize substances which he said he had reason to believe resembled those present in potent liver extract. As a basis for the selection of the materials used in his experiments he employed the reaction with alkaline solution of trinitrophenol. A positive reaction consists of the reddening of the solution by the test substance after ten to fifteen minutes of heating in a boiling water bath. The gastric content of normal persons during fasting gave a positive reaction, whereas that of persons with pernicious anemia did not. Likewise all purified preparations active against pernicious anemia yielded a positive reaction to trinitrophenol. Because some of the properties of liver extract suggest that its activity may depend on a phenomenon of oxidation-reduction and that the essential substances involved may be an aldehyde derivative and dextrosamine, Jacobs employed intramuscular and subcutaneous injections of these substances in the treatment of patients with pernicious anemia in relapse. When either substance was given alone no reticulocyte response was obtained, but in 1 case he obtained a reticulocyte count of 14 per cent five days after the subcutaneous injection of a water solution of the product of interaction between acetaldehyde and dextrosamine. Three other previously untreated patients failed to respond to this treatment. Jacobs [19] has isolated a crystalline substance from liver extract which he concluded

17. Jacobson, B. M., and Subbarow, Y.: Studies of the Principle in Liver Effective in Pernicious Anemia; Therapeutic Activity of Its Multiple Factors, J. Clin. Investigation **16**:573, 1937.

18. Jacobs, H. R.: On the Nature of the Antipernicious Anemia Principle, J. Lab. & Clin. Med. **22**:371, 1937.

19. Jacobs, H. R.: On the Nature of the Antipernicious Anemia Principle: II. Identification of the 5, 6-Quinone of Dihydroindole-2-Carboxylic Acid in Liver Extract, J. Lab. & Clin. Med. **22**:890, 1937.

is identical with the 5,6-quinone of dihydroindole-2-carboxylic acid obtained by Rafer from the reactions of tyrosinase and tyrosine. Because this substance is difficult to synthesize in pure form, Jacobs [20] employed in the treatment of 1 patient with pernicious anemia the "red substance" obtained from the action of tyrosinase on tyrosine in the presence of oxygen. The reticulocyte response was equivocal but sufficiently suggestive of activity to warrant further trial.

The fact that some patients with pernicious anemia respond much more favorably to the parenteral injection of liver extract than to its oral administration led Helmer and Fouts [21] to attempt to measure the absorptive ability of the intestinal tract by estimations of the urinary excretion of xylose. This sugar is not metabolized and is believed to pass through the liver unchanged and to escape from the body through the kidneys. The authors were unable to demonstrate in patients with pernicious anemia a consistent abnormality in the absorption of xylose from the alimentary tract. However, owing to the great difference between the molecular weight of the active principle of liver and that of xylose, the authors concluded that ability to absorb xylose does not necessarily parallel the absorptive capacity for the antianemic principle. Fouts, Helmer and Zerfas [22] studied the secretion of hippuric acid in cases of pernicious anemia after the injection of sodium benzoate. This test is regarded as a measure of the detoxifying function of the liver. In their cases there was no obvious correlation between the level of the red blood cell count and the amount of hippuric acid secreted by the kidneys. There was, however, a direct relation between the quantity recovered from the urine and the renal function as measured by the urea clearance test. They concluded that both decreased secretion of hippuric acid and increased requirement of liver extract for maintenance of normal blood values are the result of complicating factors such as senility, infection and changes in the spinal cord. Impaired hepatic function, as indicated by the decreased ability of the liver to conjugate benzoic acid, had no apparent influence on the maintenance requirement of liver extract.

The problem of bioassay of preparations proposed for the treatment of pernicious anemia has attracted a number of investigators. Among the animal tests suggested during recent years is the reticulocyte

20. Jacobs, H. R.: On the Nature of Anti-Pernicious Anemia Principle: Response of a Case of Pernicious Anemia to the Oral Administration of Tyrosinase-Tyrosine Mixture, J. Lab. & Clin. Med. **22**:892, 1937.

21. Helmer, O. M., and Fouts, P. J.: Gastrointestinal Studies: Excretion of Xylose in Pernicious Anemia, J. Clin. Investigation **16**:343, 1937.

22. Fouts, P. J.; Helmer, O. M., and Zerfas, L. G.: Secretion of Hippuric Acid in Pernicious Anemia, Am. J. M. Sc. **193**:647, 1937.

response of normal stabilized guinea pigs to the administration of potent antianemic material. This test, formulated and employed by Jacobson, has not met with general favor. After careful studies Hummel [23] concluded that the percentage of reticulocytes in the circulating blood of the guinea pig increases after a variety of disturbances, such as dietary changes, pregnancy, injury and infection. Occasionally rises occur for which no cause can be found. By suitable care in handling and feeding, stable reticulocyte levels may be maintained for as long as three months. It was possible to demonstrate increases in the reticulocyte count after the oral administration of a potent liver extract, and such responses did not occur when the active principle had been destroyed. However, the author said he did not believe that his observations proved the validity of the guinea pig reticulocyte test for the therapeutic activity of liver preparations, since the question of which constituent of liver is effective in producing the response must await further investigation. Even less satisfactory results with the guinea pig assay method were reported by Bachrach and Fogelson.[24] From their observations and from a review of the literature they concluded that no animal can supplant the human being with pernicious anemia as a basis for the assay of potency of substances against pernicious anemia.

Evidence against the efficacy of parenteral injections of congo red, both in the induction of remissions and in the maintenance therapy of patients with pernicious anemia, was reported by Lendvai [25] and by Barker.[26] After extensive observations both investigators concluded that the dye is totally ineffective in the treatment of patients with pernicious anemia.

Granady [27] reported 4 cases of pernicious anemia occurring in Negroes and said that the condition is not as rare in this race as has been commonly supposed. His patients appeared to have all the signs and symptoms necessary to establish the diagnosis of pernicious anemia, and in addition each showed a satisfactory response after the administration of specific therapy. No mention was made as to whether or

23. Hummel, L. E.: Liver Extract and Reticulocytosis in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **36**:657, 1937.

24. Bachrach, W. H., and Fogelson, S. J.: Effect of Anti-Pernicious Anemia Substances upon Guinea Pig Reticulocytosis and a Review of the Literature, J. Lab. & Clin. Med. **22**:925, 1937.

25. Lendvai, J.: Die Wirkung von Kongorot bei perniziöser Anämie, Klin. Wchnschr. **15**:1034, 1936.

26. Barker, W. H.: Congo Red in Treatment of Pernicious Anemia and Sprue, Am. J. M. Sc. **194**:293, 1937.

27. Granady, J. T. W.: Pernicious Anemia in Negro with Report of Four Cases, J. Nat. M. A. **29**:9, 1937.

not the patients were mulattoes. It is not so rare to observe pernicious anemia in persons with a mixture of white and Negro strains, but the occurrence of the disease in one of proved pure Negro stock is difficult to substantiate.

Five patients with pernicious anemia were studied by Stewart, Crane and Deitrick [28] in order to observe the adjustment of the heart to a slowly developing decrease in the oxygen capacity of the blood. Observations of the cardiac output determined by the acetylene method were made during the stage of anemia and were repeated during a therapeutically induced remission. Their findings were as follows:

> During the anemic state the cardiac output, the heart rate, and the oxygen consumption were in all cases elevated, and the circulation time short. As the anemia became less, the cardiac output, the heart rate, and the oxygen consumption decreased, and the circulation time increased, all approaching more nearly normal values.

From these observations the authors concluded that during the stage of anemia in pernicious anemia the heart is required to circulate an increased amount of blood per minute. The amount of the increase is inversely proportional to the concentration of hemoglobin.

Stalker [29] reviewed the literature dealing with the occurrence of angina pectoris in patients with pernicious anemia and reported a single case. Statistics were cited to indicate that this is not a common complication, since a study of large groups of patients with pernicious anemia showed that only 2 to 3 per cent had angina. As the two diseases occur in the same age groups, it is not surprising that they should have a coincidental coexistence. Although the author said he recognized that anoxemia resulting from anemia diminishes the function of the myocardium and so furthers the occurrence of anginal attacks, he said he believed that anemia alone cannot cause angina pectoris but that in addition there must always be disease of the coronary arteries. The findings in the case reported substantiate this view.

McGregor [30] described 2 patients with pernicious anemia and diabetes mellitus and reviewed the literature concerning the coexistence of the two diseases. He quoted figures which indicate that between 0.5 and 1 per cent of all patients with pernicious anemia also have diabetes. In explaining why the two diseases may exist in the same

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28. Stewart, H. J.; Crane, N. F., and Deitrick, J. E.: Studies of Circulation in Pernicious Anemia, J. Clin. Investigation **16**:431, 1937; abstracted, Tr. A. Am. Physicians **51**:84, 1936.

29. Stalker, H.: Angina Pectoris and Pernicious Anemia (Old Terminology): Résumé of the Literature, with a Case Report, Ann. Int. Med. **10**:1172, 1937.

30. McGregor, H. G.: Pernicious Anemia with Diabetes Mellitus, Brit. M. J. **2**:617, 1937.

patient he referred to Root, who has pointed out factors which may predispose to their combined incidence, as follows: Achlorhydria, which is practically always present in cases of pernicious anemia, is not a rare finding in cases of diabetes; diabetes occurs most commonly in the same age groups as does pernicious anemia, and, finally, the familial tendency is well recognized in both diseases. In spite of a certain amount of common ground between the two conditions, the authors said they regarded this association as one of chance.

*Changes in the Blood and Bone Marrow.*—Schiødt,[31] following the work of Riddle, applied Robertson's simple growth equation to the regeneration of erythrocytes in pernicious anemia and in other types of anemia. The curve of regeneration during treatment with desiccated stomach or liver extract is, in general, in accord with the growth equation, although a temporary end point somewhat lower than the normal level of the red blood corpuscles must be assumed. Ornstein and Schouten[32] studied the duration of life and mode of death of erythrocytes in patients with pernicious anemia before and after treatment with liver. The mean age of the cells during relapse is much less than that in remission. In the former state the anomalous cells have a mortality rate practically independent of their age, and their destruction is random and fortuitous. Normal individual corpuscles, on the other hand, are destroyed at an age closely approximating their mean span of life.

On the assumption that the action of the antianemic principle is concerned with the formation of erythrocyte stroma rather than hemoglobin synthesis, Williams and his colleagues[33] studied the chemical composition of the cells and plasma before and after treatment. They found that the sodium, potassium and chlorine contents of the serum and erythrocytes were unaffected in pernicious anemia. However, during relapse there was an increased amount of neutral fat in the serum, with an associated deficiency of cholesterol esters and phospholipid. The lipid values returned to normal after treatment. A study of erythrocytes showed that they contained an excessive amount of cholesterol esters and a deficiency of phospholipid and free cholesterol. Both the cation and the anion content were elevated, the former being due chiefly to the increased potassium and the latter to a greater hemoglobin con-

31. Schiødt, E.: Regeneration of Blood, Expressed by Simple Equation, Acta med. Scandinav., 1936, supp. 78, p. 195.

32. Ornstein, L. S., and Schouten, J. F.: The Duration of Life and the Mode of Death of Erythrocytes Before and After the Treatment of Pernicious Anemia with Liver, Nederl. tijdschr. v. geneesk. **81**:1717, 1937.

33. Williams, H. H., and others: Lipid and Mineral Distribution of Serum and Erythrocytes in Pernicious Anemia Before and After Therapy, J. Biol. Chem. **118**:599, 1937.

tent. During remission both the lipid and the mineral content of the red blood cells became normal. The authors suggested that the chemical composition of the abnormal erythrocytes in pernicious anemia during relapse indicates that the cells not only are in a state of lowered function but are in process of degeneration and retrogression.

Bang and Ørskov [34] studied the permeability of the red blood cells to dextrose in 10 patients with pernicious anemia, and in 7 the permeability was tested periodically during the course of treatment. They found that during relapse the permeability of the erythrocytes is increased to as much as four times the average normal value. When the anemia disappears as a result of treatment, the permeability becomes normal. The explanation of the changes during treatment is uncertain, but the following factors should be considered: (1) an alteration in the membrane of the circulating red blood cells, (2) the formation of large numbers of young red blood cells with low permeability and (3) a diminished destruction of red blood cells, with a resultant rise in the average age of the circulating erythrocytes.

The production and excretion of bile pigment in pernicious anemia may be due to increased rate of destruction of hemoglobin, or it may result from partial or total pathologic metabolism of the precursors of hemoglobin. In order to investigate this problem Dobriner and Barker [35] studied the excretion of coproporphyrin I of a patient with pernicious anemia in relapse and during the return of the red blood cells and hemoglobin to normal. They demonstrated a definite increase in the amount of coproporphyrin I in the urine and feces during relapse and found that lower values were present when the blood reached normal limits. These observations suggested to the authors that in pernicious anemia there is an increase in the production of coproporphyrin I proportional to an increased formation of type III porphyrin rather than a pathologic production resulting in a disturbed ratio between the formation of type I and that of type III compounds.

Weil [36] said he believed that in pernicious and other hyperchromic anemias there is a familial, hereditary or acquired "hematic soil," characterized by a pathologic tendency of both the bone marrow and the upper portion of the gastrointestinal tract. A similar mechanism is claimed for *aleucie hémorrhagique* and total medullary aplasia.

34. Bang, O., and Ørskov, S. L.: Variations in the Permeability of Red Blood Cells in Man, with Particular Reference to Conditions Obtaining in Pernicious Anemia, J. Clin. Investigation **16**:279, 1937; Hospitalstid. **80**:141, 1937.

35. Dobriner, K., and Barker, W. H.: Total Coproporphyrin I Excretion in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **36**:864, 1937.

36. Weil, P. E.: Le terrain morbide dans le Biermer et les états d'aplasia médullaire, Sang **11**:783, 1937.

Dameshek and Valentine [37] studied the sternal bone marrow of 20 patients with pernicious anemia before and after specific therapy. Twenty-six biopsies were done, and the results were correlated with the status of the peripheral blood and with the response to treatment. The biopsies were performed by Seyfarth's technic, in which a small trephine is employed. A definite correlation was found between the marrow and the blood picture for, generally speaking, the lower the red blood cell count, the more primitive and hyperplastic the marrow. The marrow of patients with pernicious anemia during relapse uniformly showed marked hyperplasia, with complete replacement of fat by proliferating cells. In most cases, especially those in which there was severe anemia, the hyperplasia was due primarily to a marked increase of cells of the megaloblastic series, although myeloid proliferation was also always found. There were also present large numbers of erythrogones (promegaloblasts) and sometimes even more primitive cells than those which resembled histiocytes. Little tendency toward maturation of the red blood cells was apparent, for nucleated red blood cells of the more mature types were present only in small numbers. The megakaryocytes in the blood of patients with low red blood cell counts were greatly diminished in number or were absent. When the patients received liver therapy, striking alterations occurred within twenty-four hours after treatment was begun. The marrow picture rapidly changed to one in which the normoblast was the predominating cell. There was also a disappearance of the misshapen giant polymorphonuclear neutrophils. On the other hand, observations somewhat at variance with those of Dameshek and Valentine were reported by Storti.[38] He studied the bone marrow of 4 patients with pernicious anemia at intervals before and after liver therapy. Besides the arrest at the megaloblast stage, he noted that the normoblast tissue was equal to or greater than that of normal marrow. With the approach of the height of the reticulocyte response there is a disappearance of megaloblastic tissue, and hemopoiesis proceeds by the normoblastic route. The antianemic principle, he found, does not produce a normoblastic proliferation but causes a ripening of the preexisting normoblasts and a reduction of the megaloblastic tissue.

37. Dameshek, W., and Valentine, E. H.: Sternal Marrow in Pernicious Anemia: The Correlation of Observations at Biopsy with Blood Picture and Effects of Specific Treatment in Megaloblastic ("Liver-Deficient") Hyperplasia, Arch. Path. **23**:159 (Feb.) 1937.

38. Storti, E.: Studio in vivo del midollo osseo nell'anemia perniciosa; sulle primissime modificazioni morfologico-funzionali del tessuto mieloide conseguenti a epatoterapia, Haematologica **18**:1, 1937.

Biopsy specimens of bone marrow from patients with pernicious anemia were studied by Jones [39] with particular reference to the origin and development of neutrophils. He concluded that in pernicious anemia during relapse there is panmyelopathy. The proliferation of megaloblasts in this disease is regarded as a pathologic developmental form, rather than the result of inhibition of maturation at the megaloblast stage, which is the more common view held in this country. In confirmation of Storti's observations, Jones found evidence of actual increase in the total number of normoblasts in the marrow of patients with pernicious anemia, and he concluded that there is inhibition of maturation of these cells. Alterations in the neutrophils, hyperpolymorphism, hypersegmentation and gigantism are not considered as degenerative manifestations but as evidence of a pathologic neutrophil series. Likewise, the megakarocytes are pathologically altered so that there is partial failure of production of platelets. It is suggested that a lack of the antianemic principle may have its primary effect on the stem cell or even on the reticuloendothelium.

*Manifestations Due to Lesions in the Spinal Cord and Brain and Practical Therapy.*—In recent years the major problem in caring for patients with pernicious anemia has been the prevention and treatment of lesions of the central nervous system. It is generally accepted that degeneration of the spinal cord and brain is part of the disease process. Herman, Most and Jolliffe [40] studied 255 patients with pernicious anemia. Involvement of the spinal cord was present in 72.5 per cent of their cases, and psychotic changes were observed in 15.7 per cent.

In an attempt to explain the obscure etiology of the pathologic changes in the central nervous system due to anemia, Heymans and his associates [41] performed some interesting experiments on isolated perfused dog heads. They concluded that certain nerve centers, probably located in the cerebrum, are apparently necessary for continued survival of the animal. These centers are especially sensitive to anoxemia and are irreparably damaged after circulatory arrest is maintained for five minutes or longer. Although such conditions are not present in pernicious anemia, it is conceivable that prolonged anemia itself may aid in the production or development of pathologic changes in the cen-

39. Jones, O. P.: Origin of Neutrophiles in Pernicious Anemia (Cooke's Macropolycytes): Biopsies of Bone Marrow, Arch. Int. Med. **60**:1002 (Dec.) 1937.

40. Herman, M.; Most, H., and Jolliffe, N.: Psychoses Associated with Pernicious Anemia, Arch. Neurol. & Psychiat. **38**:348 (Aug.) 1937.

41. Heymans, C.; Bouckaert, J. J.; Jourdan, F.; Nowak, S. J. G., and Farber, S.: Survival and Revival of Nerve Centers Following Acute Anemia, Arch. Neurol. & Psychiat. **38**:304 (Aug.) 1937.

tral nervous system. However, anemia cannot be regarded as the sole cause of the degeneration of the nervous tissue. Woltman and Heck [42] pointed out that funicular degeneration of the spinal cord may exist in at least sixty conditions other than pernicious anemia. Golden [43] emphasized the importance of diet in the prevention of nervous disorders and discussed the role of various food factors both in the production and in the treatment of these disorders. Some evidence supporting the relation of food metabolism and degeneration of the spinal cord may be gained from the case report of Lacroix and Koek.[44] They observed the development of macrocytic anemia and manifestations of involvement of the spinal cord in a patient nine years after extensive resection of the stomach. Satisfactory improvement was obtained with parenteral administration of liver extract and vitamin B therapy.

Conclusions drawn from apparent therapeutic results should be guarded, as it is known that spontaneous variations occur in the intensity of the neurologic manifestations without any medication. It is generally agreed that adequate antianemic therapy is of primary importance in the treatment of lesions of the spinal cord. Criteria of adequacy include elevations of erythrocyte and hemoglobin values to normal levels and maintenance of the normal size of the red blood cell. Hitzenberger [45] advocated massive doses of both liver and stomach preparations and recommended the use of supplementary vitamins. In addition to medicinal therapy, Hyland and Farquharson [46] recommended long periods of rest. In their opinion the combination of adequate medication and prolonged rest prevents changes in the central nervous system, it arrests the progress of any existing pathologic condition of the cord and it effects considerable improvement, especially in anemia of short duration.

Moench [47] studied a group of 32 patients with pernicious anemia to determine the amount of therapy necessary to maintain the red blood cell count at a normal level and the length of time required to bring

42. Woltman, H. W., and Heck, F. J.: Funicular Degeneration of the Spinal Cord Without Pernicious Anemia, Arch. Int. Med. **60**:272 (Aug.) 1937.

43. Golden, L. A.: The Role of Diet in Nervous Diseases, New Orleans M. & S. J. **90**:73, 1937.

44. Lacroix, W., and Koek, H. C.: Case of Hyperchromic Anemia with Neurologic Symptoms Developing After Resection of Stomach, Nederl. tijdschr. v. geneesk. **81**:2221, 1937.

45. Hitzenberger, K.: Zur Behandlung der neurologischen Komplikationen der Anaemia Perniciosa, Wien. med. Wchnschr. **87**:257, 1937.

46. Hyland, H. H., and Farquharson, R. F.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, Arch. Neurol. & Psychiat. **36**:1166 (Dec.) 1936.

47. Moench, L. M.: Variations in Response to Therapy in Pernicious Anemia, Ann. Int. Med. **10**:1115, 1937.

the count to 4,500,000 per cubic millimeter. The average length of the maintenance period was twenty-one months, the shortest period being five and the longest fifty months. Therapy consisted of the intramuscular injection of an average monthly dose of the amount of a commercially prepared concentrated liver extract derived from 300 Gm. of liver or unconcentrated extract obtained from 200 Gm. of liver prepared in the laboratories of the New York Hospital. This dosage maintained the red blood cells of 70 per cent of the patients above the minimum normal red blood cell level of 4,900,000 for men and 4,400,000 for women. The red blood cell counts of the remaining 30 per cent of these patients were only slightly reduced, varying between 3,600,000 and 4,600,000 for 5 men and between 3,900,000 and 4,200,000 for 5 women. In 8 of this group the disease appeared to be fully controlled as far as symptoms and signs were concerned. In 1 patient there was slow progression of changes in the central nervous system, and in another there was no relief from the symptoms of which he had originally complained. All the women and 3 of the men received approximately twice the usual amount of intramuscular therapy, and 2 received supplementary liver orally. On the other hand, the author reported that for 1 patient the blood was maintained at a normal level for a year in spite of the fact that he was receiving intramuscularly the extract derived from only 150 Gm. of liver. Since this followed a period of heavy dosage the author said he considered it as evidence of gradual storage of active principle which subsequently yields a hemopoietic effect.

Observations were also made by Moench to determine the time required for the erythrocyte count to reach 4,500,000 and the amount of liver preparation used. Fifteen of the 33 patients, with an average initial red blood cell count of 2,600,000, received by intramuscular injection the amount of extract derived from an average of 670 Gm. of liver, and the red cell count reached 4,500,000 in two months or less. There were 11 patients with an average initial count of 1,900,000 for whom more than two months but less than three months was required before this level was reached. They received intramuscularly the extract derived from an average of 1,072 Gm. of liver. A third group, consisting of 7 patients, required from four to nine months for the red blood cells to attain a level of 4,500,000. They received intramuscularly the extract derived from 900 to 6,600 Gm. of liver. For some of these patients the dosage was considered insufficient; others were suffering from senility, malnutrition, depressions or infection, such as sinusitis. It was emphasized by the author that symptoms referable to the nervous system are the most serious and persistent.

In slightly over half the patients there was subjective improvement. Seventeen of 26 patients who had objective changes of the nervous system showed "apparent improvement" as judged by the clinic records. Such a high percentage of patients showing objective evidence of improvement in the manifestations of involvement of the central nervous system is not in accord with the observations of other clinicians.

Hartfall [48] reported therapeutic results for 16 patients with pernicious anemia in relapse and 20 patients receiving maintenance treatment. Intramuscular injections of a concentrated liver extract, 1 cc. derived from 100 Gm. of liver, were employed exclusively. In all cases 2 to 5 cc. of this preparation produced a satisfactory reticulocyte response. Subsequent treatment with 1 to 2 cc. at weekly intervals sufficed to elevate the red blood cell count to 4,000,000 or above in twenty-one to thirty-five days except in cases of anemia complicated by infection. Satisfactory maintenance treatment consisted of the administration of 1 cc. of the concentrated extract at intervals varying from three to eight weeks. Individual variations of maintenance requirement were emphasized by the author. The incidence and the severity of neurologic lesions of the patients in Hartfall's series were relatively slight. Improvement in nervous symptoms was noted after induction of remission in the few cases in which there was involvement of the central nervous system.

Mulholland [49] reported a case of pernicious anemia in a man aged 62 in whom there was a prompt and characteristic response to the intramuscular injection of liver extract. After a subsequent relapse, attributed to inadequate dosage of liver extract, he was treated with 32 cc. of potent extract by intramuscular injection over forty-five days and received in addition stomach U. S. P. for ten days and liver by mouth for thirty days of this period. During this time no significant reticulocyte response occurred, and there was a decline of both red blood cells and hemoglobin. Subsequently, he was given five intravenous injections each of 20 cc. of liver extract derived from 100 Gm. of liver. After forty days the erythrocyte count was 4,500,000 and the hemoglobin value 76 per cent. Maintenance of these values was then effected by the intramuscular injection of 2 cc. of liver extract per week. No explanation of the lack of response to intramuscular therapy is offered. Failure to absorb the intramuscular preparation seems unlikely in view of the subsequent satisfactory control of the condition with this mode of therapy.

48. Hartfall, S. J.: Experiences with Concentrated Whole Liver Extract, Lancet **2**:317, 1937.

49. Mulholland, H. B.: Intravenous Liver Extract in Therapy of Pernicious Anemia: Report of a Case, Ann. Int. Med. **11**:671, 1937.

Sellers [50] made the statement that prior to the introduction of liver in the treatment of pernicious anemia the average duration of life after the diagnosis was made was estimated at two to two and one-half years. Now it is generally agreed that with proper liver therapy the fatal termination may be postponed indefinitely in a majority of cases. He quoted Stocks as stating that since 1926, when liver treatment was introduced, there has been "an average lengthening of life of all persons affected with pernicious anemia in England and Wales of about three to three and one-half years." This does not give the true life expectancy, because it includes persons who were adequately treated as well as those who, for one reason or another, failed to receive adequate specific treatment prior to the terminal illness. The author pointed out that wide differences in mortality from pernicious anemia exist throughtout the world for reasons which are not apparent. For example, in 1926 the mortality rate in Norway was 5.4 and in Ontario during the same year the rate was 15.9 per hundred thousand. In the countries where data were obtained (Norway, the United States, New Zealand, England, Wales, Scotland, Canada and the province of Ontario) there was an abrupt drop in the mortality rate in 1927, coinciding with the general use of liver in the treatment of the disease. This reduction has been well maintained. In Ontario, for example, the standardized specific mortality in 1934 was only 47 per cent of the average level for the period prior to the introduction of liver therapy. The reduction of mortality has been apparent in all age groups up to 70 years, but it has been most marked in youth. Sellers concluded:

> Comparison of the actual average age at death of persons dying of pernicious anemia in Ontario with that to be "expected" on the basis of specific mortality experience in the period prior to liver therapy, 1921-1926, shows that the net increase in the average age of death amounted in 1934 to 5.3 years in males and to 5.1 years in females.

During the period from 1921 to 1935, inclusive, there were 6,223 deaths from pernicious anemia among the policy holders of the Metropolitan Life Insurance Company (Dublin and Lotka [51]), an incidence of 0.3 per cent of all deaths; there were 1,787 white males, 150 Negroes, 4,015 white females and 271 Negresses. The death rate from pernicious anemia was 2.5 per hundred thousand.

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50. Sellers, A. H.: A Study of the Objective Efficacy of Liver Therapy in Pernicious Anemia Based on Recorded Mortality Data, Am. J. Hyg. **25**:259, 1937.

51. Dublin, L. I., and Lotka, A. J.: Twenty-Five Years of Health Progress: A Study of the Mortality Experience Among the Industrial Policyholders of the Metropolitan Life Insurance Company 1911 to 1935, New York, Metropolitan Life Insurance Co., 1937, p. 533.

MACROCYTIC ANEMIA OTHER THAN PERNICIOUS ANEMIA

Recent reviews by Goldhamer and his associates [52] and by Brown [53] emphasized some of the etiologic factors which may lead to macrocytic anemia. A substance necessary for the maturation of red blood cells is produced apparently by the interaction of a dietary and a gastric intrinsic factor. The product so formed is absorbed from the intestine; it passes through and is modified by the liver and is utilized by the bone marrow as needed. Macrocytic anemia will result if there is disturbance of any of the steps involved in this mechanism.

Thus far the extrinsic factor has not been identified. Elsom [54] observed the development of macrocytic anemia in pregnant women receiving a diet deficient in vitamin B. The anemia responded readily to the addition of yeast or to the intramuscular administration of liver extract. Two patients with features simulating pernicious anemia who had received a deficient diet for a long time were described by Groen and Snapper.[55] Both secreted free hydrochloric acid, but the quantity of gastric juice was decreased. One responded to liver therapy and the other to autolyzed yeast. The authors concluded that the macrocytic anemia in these cases was the result of a deficiency of the extrinsic factor.

Langmead and Doniach [56] described the case of a 13 month old child who, they believed, showed the necessary requirements for a diagnosis of pernicious anemia. The development of pernicious anemia in a woman who drank nitric acid was reported by Alsted.[57] In his opinion the atrophy of the gastric mucosa due to the nitric acid resulted in failure of production of the intrinsic factor. Lake [58] reviewed reports of 320 cases in which gastrectomy had been performed for various causes. In none of these cases did macrocytic anemia develop, although an occasional case of microcytic anemia was observed. In 4 of a series

52. Goldhamer, S. M.; Bethell, F. H.; Isaacs, R., and Sturgis, C. C.: Blood: A Review of the Recent Literature, Arch. Int. Med. **59**:1051 (June) 1937.

53. Brown, C. L.: Clinical Features of Macrocytic Anemias, Pennsylvania M. J. **40**:922, 1937.

54. Elsom, K. O.: Macrocytic Anemia in Pregnant Women with Vitamin B Deficiency, J. Clin. Investigation **16**:463, 1937.

55. Groen, J., and Snapper, I.: Dietary Deficiency as a Cause of Macrocytic Anemia, Am. J. M. Sc. **193**:633, 1937.

56. Langmead, F. S., and Doniach, I.: Pernicious Anemia in an Infant, Lancet **1**:1048, 1937.

57. Alsted, G.: Pernicious Anemia After Nitric Acid Corrosion of the Stomach, Lancet **1**:76, 1937.

58. Lake, N. C.: Partial Gastrectomy: A Review of Three Hundred and Twenty Cases, Brit. M. J. **2**:49, 1937.

of 40 patients studied for five to twelve years after gastric resection for ulcer, Manizade [59] noted macrocytic anemia.

In 1936 Israels and Wilkinson described a syndrome characterized by macrocytic anemia, free hydrochloric acid in the gastric contents, hyperplastic bone marrow and failure of response to antianemic therapy. The case of a 19 year old boy who exhibited all the features of this syndrome was reported by Abrahamson and Thompson,[60] who attributed the anemia to an intrinsic defect of the bone marrow. Wilkinson, Klein and Ashford [61] demonstrated the presence of the hemopoietic substance in the livers of patients who died as a result of achrestic anemia. In their opinion, such anemia results from failure of the marrow to utilize the erythrogenic material.

Macrocytic anemia has been produced in animals by various methods. Rhoads [62] fed indole to dogs on a deficient diet and observed hyperplasia of the marrow and macrocytic anemia. Liver extract was of both preventive and curative value. Substituting aminopyrine for indole, Rhoads and Miller [63] also succeeded in producing macrocytic anemia in dogs. Campanacci and Tosi [64] observed in rabbits after injections of hydroquinone, resorcinol, phenol or thyroxin, macrocytic anemia which could be prevented or cured by the parenteral administration of liver extract.

Mettier and Purviance [65] failed to produce macrocytic anemia in gastrectomized dogs by administering a diet deficient in vitamin $B_2$, and they were not able to influence the microcytic anemia resulting from

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59. Manizade, M. D.: Zur Frage der Anämie nach Magenresektion (Das Blutbild bei 40 magenresezierten Kranken, 5 bis 12 Jahre nach der Operation wegen Ulcus ventriculi oder duodeni), Wien. klin. Wchnschr. **50**:1455, 1937.

60. Abrahamson, L., and Thompson, A.: Achrestic Anaemia, Irish J. M. Sc., February 1937, p. 66.

61. Wilkinson, J. F.; Klein, L., and Ashford, C. A.: Haemopoietic Activity of the Human Liver: Achrestic Anaemia and Aplastic Anemia, Quart. J. Med. **6**:143, 1937.

62. Rhoads, C. P.: Effect of Indol on Hematopoiesis in Dogs Fed Deficient Diets, Proc. Soc. Exper. Biol. & Med. **36**:652, 1937.

63. Rhoads, C. P., and Miller, D. K.: Effect of Diet on Susceptibility of Canine Hematopoietic System to Damage by Amidopyrine, Proc. Soc. Exper. Biol. & Med. **36**:654, 1937. Miller, D. K., and Rhoads, C. P.: The Effect of Diet on the Susceptibility of the Canine Hematopoietic Function to Damage by Amidopyrine, J. Exper. Med. **66**:367, 1937.

64. Campanacci, D., and Tosi, S.: L'azione dell'epatoterapia nelle anemie tossiche sperimentali da sostanze aromatiche, Gior. di clin. med. **18**:391, 1937.

65. Mettier, S. R., and Purviance, K.: Effect of Artificial Achylia Gastrica and a Diet Restricted in Vitamin $B_2$ (G) on Hematopoiesis, Proc. Soc. Exper. Biol. & Med. **36**:429, 1937.

removal of the stomach. Hyperchromic anemia in swine following gastrectomy was reported by Waterman, Kok and Hirschfeld.[66] The anemia was favorably influenced by the parenteral use of liver extract.

### ANEMIA ASSOCIATED WITH OTHER DISEASE ENTITIES

*Hemolytic Anemia.*—The change in the size and the shape of the red blood cells in familial hemolytic icterus is considered by many to be a hereditary manifestation. Dedichen[67] cited the history of 18 members of two families in support of this view. Some writers are of the opinion that the alteration in the erythrocytes is due to lessened vitality of the cells; others believe that there is a primary defect of the bone marrow, and, finally, some suggest that the small red blood cells and the increased fragility are phenomena of regeneration secondary to the increased activity of the bone marrow. The disease may occur in either sex, it has no racial distribution and it is transmitted by both males and females.

Roentgenographic details of osseous changes, not uncommonly associated with this condition, have been described by Caffey.[68] In the opinion of Acuña,[69] such alterations of the bones accompanying hemolytic anemia constitute a new disease that is probably related to the erythroblastic anemia of infancy.

Since the treatment of familial hemolytic icterus is specific, it is important to differentiate this condition from other types of hemolytic anemia. The latter can often be corrected with transfusions or by the elimination of specific drugs[70] or allergens.[71] Groag[72] has pointed out that roentgen therapy is of no value in the treatment of the familial

66. Waterman, L.; Kok, D. J., and Hirschfeld, W. K.: Experimental Hyperchromic Anemia After Gastric Resection, Nederl. tijdschr. v. geneesk. **81**:2622, 1937.

67. Dedichen, H. G.: Epidemic Occurrence of Anemic Crises in Hemolytic Jaundice, Norsk mag. f. lægevidensk. **98**:279, 1937.

68. Caffey, J.: Skeletal Changes in the Chronic Hemolytic Anemias (Erythroblastic Anemia, Sickle Cell Anemia and Chronic Hemolytic Icterus), Am. J. Roentgenol. **37**:293, 1937.

69. Acuña, M.: Alteraciones radiológicas del esqueleto en la ictericia hemolítica Congénita, Prensa méd. argent. **24**:1878, 1937.

70. (*a*) Kohn, S. E.: Acute Hemolytic Anemia During Treatment with Sulfanilamide, J. A. M. A. **109**:1005 (Sept. 25) 1937. (*b*) Harvey, A. M., and Janeway, C. A.: Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide, ibid. **109**:12 (July 3) 1937.

71. Hutton, J. E.: Favism: An Unusually Observed Type of Hemolytic Anemia, J. A. M. A. **109**:1618 (Nov. 13) 1937.

72. Groag, P.: Ueber einen Versuch, den Blutbefund bei einem Fall konstitutioneller hämolytischer Anämie durch Kurzwellenbestrahlung der Milz zu beeinflussen, Wien. klin. Wchnschr. **50**:502, 1937.

type. Sharpe [73] reported unsatisfactory results with iron and liver. It is generally agreed that splenectomy is desirable especially for patients who show marked anemia or who are subject to severe relapses. Although the anemia is corrected and the icterus disappears after removal of the spleen, microcytosis, spherocytosis and increased fragility persist. Resistance to hypotonic salt solution may increase after operation, but it does not become normal. Gordon, Kleinberg and Ponder [74] attributed the change in resistance after splenectomy to a modification of the structure of the envelop of the red blood cell.

*Changes in the Blood Associated with Infection.*—Infection may cause a disturbance in the balance between the production and the destruction of the red blood cells. Usually hypochromic and microcytic anemia results, although macrocytic anemia is not uncommon. Gwyn [75] described such anemia associated with rheumatic infection. Giordano and Blum [76] reported 3 cases of acute hemolytic anemia (Lederer's type) and summarized reports of 52 other cases. They stated that the disease can occur at any age and in either sex. Its onset is usually sudden and is characterized by headaches, gastrointestinal upsets, abdominal pain and, after an incubation period of two to six days, severe anemia, pallor, icterus and fever. There may or may not be splenic or hepatic enlargement. Free acid is present in the gastric juice, there is no glossitis and the disease runs a rapid course. The anemia is macrocytic, with some evidence of regeneration. Leukocytosis with a leukemoid reaction is most common, but leukopenia may occur. Hyperbilirubinemia is present, associated with an increase in the excretion of urobilin and the appearance of free hemoglobin in the urine. The fragility of the red blood cells is within normal limits. Although infection is the suspected etiologic factor, it is not proved. Blood transfusions provide the only satisfactory means of treatment.

Studies of the blood in acute rheumatic fever were made by Massell and Jones.[77] Although leukocytosis usually remained after the clinical manifestations had subsided, a normal white blood cell count might accompany clinical signs of active rheumatic fever. The authors concluded that the leukocyte count is nonspecific but that when it is elevated,

73. Sharpe, J. C.: Hemolytic Jaundice, Internat. Clin. **2**:146, 1937.

74. Gordon, A. S.; Kleinberg, W., and Ponder, E.: Decreased Red Cell Fragility After Splenectomy, Am. J. Physiol. **120**:150, 1937.

75. Gwyn, N. B.: Macrocytic Anaemia Associated with Rheumatic Infection, Canad. M. A. J. **37**:117, 1937.

76. Giordano, A. S., and Blum, L. L.: Acute Hemolytic Anemia (Lederer Type), Am. J. M. Sc. **194**:311, 1937.

77. Massell, B. F., and Jones, T. D.: Evaluation of the Signs of Active Rheumatic Fever, with Especial Reference to the Erythrocyte Sedimentation Rate and Leukocyte Count, New England J. Med. **215**:1269, 1936.

in the absence of other known cause, subclinical rheumatic fever should be suspected. Rae [78] reemphasized the importance of a high white blood cell count in coronary heart disease. Pearson and Newns [79] called attention to an unusual leukocytosis occurring in connection with whooping cough.

The hematologic findings in chronic ulcerative colitis and their relation to prognosis and treatment were studied by Garvin and Bargen.[80] They concluded that leukocytosis is uncommon in this disease and that when present it is indicative of some complication. Both the cytoplasmic and the nuclear changes might be used as indexes of the severity and the prognosis of the disease process.

Corwin [81] observed the cytologic response of the peritoneum of rabbits after injections of Bargen's vaccine and variable amounts of ricinoleate. An increase in the total number of cells occurred after twelve to twenty-four hours, affecting first the neutrophils and later, within forty-eight hours, the monocytes.

The total white blood cell count not only is of diagnostic and prognostic value in infections but is also an important aid in the study of allergic conditions. Squier and Madison [82] stated that eosinophilia and a reduction of the total number of white blood cells followed with equal frequency the ingestion of allergenic foods. They concluded that the simultaneous enumeration of eosinophils and total white blood cells enhances the value of the leukopenic index. Zeller [83] reemphasized the importance of the leukopenic index in the study of allergy and stressed the necessity of counting the white blood cells under identical conditions.

*Anemia Associated with Cancer.*—Anemia may or may not be a complication of cancer. Such anemia may be macrocytic or microcytic. Leukocytosis is usually present. The differential diagnosis between pernicious anemia and carcinoma of the stomach may be difficult when the latter is associated with macrocytic anemia. Held and Goldbloom [84]

78. Rae, M. V.: Coronary Aneurysms with Thrombosis in Rheumatic Carditis, Arch. Path. **24**:369 (Sept.) 1937.

79. Pearson, W. J., and Newns, G. H.: Extreme Degree of Leucocytosis in Whooping Cough, Lancet **2**:254, 1937.

80. Garvin, R. O., and Bargen, J. A.: Hematologic Picture of Chronic Ulcerative Colitis: Its Relation to Prognosis and Treatment, Am. J. M. Sc. **193**:744, 1937.

81. Corwin, W. C.: Peritoneal Cytologic Response: Experimental Study, Am. J. M. Sc. **193**:251, 1937.

82. Squier, T. L., and Madison, F. W.: Hematologic Response in Food Allergy: Eosinophilia in the Leucopenic Index, J. Allergy **8**:250, 1937.

83. Zeller, M.: Leucopenic Index, Am. J. M. Sc. **193**:652, 1937.

84. Held, I. W., and Goldbloom, A. A.: Carcinoma of Stomach in a Cured Case of Addison-Biermer's (Pernicious) Anemia, J. A. M. A. **108**:1398 (April 24) 1937.

reported the case of a man with pernicious anemia which was maintained in remission for several years by means of liver therapy. Gastric carcinoma subsequently developed. The authors advised careful studies of the gastrointestinal tract whenever a patient with pernicious anemia relapses while receiving adequate therapy. Because of the apparent relation between achylia, pernicious anemia and gastric carcinoma, Fabian [85] made quantitative studies of the saliva and reported a reduction in the salivary flow in these three conditions, most marked in pernicious anemia. In his opinion some association exists between the secretory glands of the stomach and the salivary glands. In an effort to differentiate pernicious anemia from the macrocytic anemia of gastric cancer, Lasch [86] devised a test to determine the amount of intrinsic factor in gastric juice. If the intrinsic factor acts as do other proteolytic enzymes, its presence in gastric contents should be demonstrable by an increase of nonprotein nitrogen in a digestive mixture. Pepsin and trypsin activity were eliminated by incubation at a $p_H$ of 5.5 to 6, which is within the active range of the intrinsic factor. Of 4 patients, 3 with proved gastric carcinoma and 1 in whom it was suspected, 2 showed absence of proteolytic enzyme activity, 1 a decrease and 1 a normal proteolytic reaction. Of 17 persons with pernicious anemia, the enzyme reaction was absent in 12; in 5 it was present in slight degree.

*Anemia Associated with Endocrine Dysfunction.*—In recent years considerable interest has been shown in the relation of the endocrines to hemopoiesis. Reich [87] offered a complete clinical and experimental summary of this association. In cases of advanced Addison's disease there is usually hypochromic anemia with lymphocytosis. Marked hypochromic anemia may also occur in the multiglandular syndromes. Often lymphocytosis is present in adiposity. After castration of animals there is reduction of the hemoglobin value and red blood cell count with accompanying leukopenia and occasional lymphocytosis. The injection of ovarian extract into castrated females has caused reduction of this lymphocytosis. In eunuchs an increase in monocytes and lymphocytes has been observed. The removal of the thymus produces little if any changes in the peripheral blood of animals, although lymphocytosis is occasionally observed. Extirpation of the parathyroid glands is often followed by increase in the total number of red blood cells. In tetany

85. Fabian, G.: Untersuchungen über die Speichelsekretion bei Magencarcinom, perniziöser Anämie und Achylia gastrica, Ztschr. f. klin. Med. **131**:403, 1937.

86. Lasch, F.: Ueber eine biochemische Methode zur quantitativen Bestimmung des "Intrinsic Factor" nach Castle im Magensaft, Klin. Wchnschr. **16**:810, 1937.

87. Reich, C.: Endocrines: Their Relation to Blood Disorders, New York State J. Med. **37**:1271, 1937.

both relative and absolute lymphocytosis have been noted. Similar findings have been observed in acromegaly. In hyperthyroidism the red blood cell count and hemoglobin value usually remain unchanged. The total leukocyte count may be normal or decreased, with accompanying relative lymphocytosis. In severe cases, an absolute increase in the lymphocyte count may occur; the eosinophil count is usually increased. Postoperatively the blood values are usually normal. Similar changes have been observed in colloid goiter. Oral administration of iodides or thyroid usually produces relative lymphocytosis; their injection may cause a temporary increase in the number of platelets, whereas insulin has the opposite effect. In patients with hypothyroidism a reduction of the red blood cell count and hemoglobin value has often been noted, with a color index usually of 1 or more. Hypochromic anemia may occur in hemachromatosis, presumably because of disturbances of iron and pigment metabolism.

Since hypothyroidism is usually associated with decreased hemopoietic activity, Limarzi, Keeton and Seed [88] induced the condition by thyroidectomy in a patient with polycythaemia vera. They stated that the blood changes were in the direction of normal. There was a perceptible decrease in the total number of red blood cells. Normal values were obtained for the total blood plasma, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Jaffé [89] discussed the association of hypothyroidism and anemia and concluded that he could not satisfactorily explain the mechanism of the blood changes.

Sharpe [90] studied a series of 20 patients with myxedema and observed anemia in 9. In 2 cases both pernicious anemia and hypothyroidism were diagnosed. He concluded that achlorhydria may facilitate the development of the anemia of myxedema but that it is not an essential etiologic factor. In his opinion defective hemopoiesis results from sluggish oxidation and can be corrected only by thyroid medication.

Guinea pigs were hypophysectomized by McFarlane and McPhail.[91] No changes were observed in the number of red blood cells or in the hemoglobin value. When solution of posterior pituitary was injected into animals both before and after operation, anemia of varying severity

88. Limarzi, L. R.; Keeton, R. W., and Seed, L.: Early Effect of Total Thyroidectomy in a Case of Polycythemia Vera (Vaquez-Osler Syndrome), Proc. Soc. Exper. Biol. & Med. **36**:353, 1937.

89. Jaffé, R. H.: Chronic Thyroiditis, J. A. M. A. **108**:105 (Jan. 9) 1937.

90. Sharpe, J. C.: Anemia of Myxedema: Its Classification and Treatment, Am. J. M. Sc. **194**:382, 1937.

91. McFarlane, W. D., and McPhail, M. K.: Pituitrin Injections and the Blood Picture in the Normal and Hypophysectomized Guinea Pig, Am. J. M. Sc. **193**: 385, 1937.

resulted. Meyer and his associates [92] hypophysectomized rats and placed them in an oxygen deficient chamber. Anemia and decrease of reticulocytes below normal invariably occurred after the operation. Unlike the observation for normal rats, exposure to reduced oxygen tension failed to produce reticulocytosis or hyperplasia of the bone marrow. When, however, the stimulus was applied within ten days after the hypophysis was removed, an increase occurred in the red blood cell count and in the hemoglobin value. No changes were observed after a lapse of twenty-five or more days after operation. Splenectomy before removal of the hypophysis did not affect the results. Liver extract was of no value in correcting the anemia. The gonadotropic substance from the urine of pregnant women (antuitrin S) produced reticulocytosis but did not alter the red blood cell count or the hemoglobin value. Thyroxin not only produced reticulocytosis but increased the number of red blood cells and the hemoglobin value. Although in the authors' opinion the pituitary gland probably affects hemopoiesis, it was concluded that there was insufficient proof of direct hormonal action. Flaks, Himmel and Zlotnik,[93] on the other hand, said they believed that a hypophysial hormone exerts control over erythropoiesis. Wilson [94] observed changes in the white blood cells of rabbits after the intravenous injection of a gonadotropic preparation. Leukocytosis usually occurred within five to eight hours and was maintained for forty-eight to seventy-two hours. There was relative and absolute increase of the polymorphonuclear leukocytes, with decrease of the other leukocytic elements. The values gradually returned to normal.

Gilman and Goodman,[95] in a series of carefully controlled experiments on dogs and rabbits, demonstrated that "pituitrin anemia" might be the result of water retention. The lowered osmotic pressure of the serum presented an abnormal environment for red blood cells and caused their destruction. The authors found that by maintenance of a normal electrolyte concentration in the serum after injections of solution of posterior pituitary, the resulting anemia could be prevented.

Achylia associated with insufficiency of the anterior lobe of the pituitary gland was observed in 5 cases by Snapper.[96] In 1 case true

92. Meyer, O. O.; Stewart, G. E.; Thewlis, E. W., and Rusch, H. P.: Hypophysis and Hematopoiesis, Folia haemat. **57**:99, 1937.

93. Flaks, J.; Himmel, I., and Zlotnik, A.: Sur l'existence d'une hormone hémopoïetique dans l'hypophyse, Presse méd. **45**:1261, 1937.

94. Wilson, D.: Effect of Anterior Pituitary-Like Hormone on the Blood Picture in Rabbits, Endocrinology **21**:96, 1937.

95. Gilman, A., and Goodman, L.: Pituitrin Anemia, Am. J. Physiol. **118**:241, 1937.

96. Snapper, I.: Relation Between Anterior Pituitary Insufficiency and the Function of the Stomach and Bone Marrow, Nederl. tijdschr. v. geneesk. **81**:265, 1937.

pernicious anemia developed, and in another anemia associated with a high color index was found. In the 3 remaining cases there was no anemia, but there was evidence of involvement of the central nervous system. It was the author's opinion that there exists a relation between the pituitary gland and the stomach, and as a result of some disturbance of this association, either the hemopoietic or the central nervous system may be affected. Snapper, Groen, Hunter and Witts [97] said they believed that the pituitary defect occurs first, followed by achlorhydria and later anemia or subacute combined degeneration. They admitted, however, that sufficient proof of this theory is lacking.

### IRON DEFICIENCY

*Retention, Transportation and Utilization of Iron.*—During recent years contributions to the knowledge of iron metabolism have come chiefly from animal studies. In contrast to the methods of animal experimentation the present trend of interest is in the direction of investigations on human subjects of the absorption of iron, its mode of transference in the body, its retention and its availability for the formation of hemoglobin. In spite of numerous studies of the intake and excretory balance of iron, there is as yet no agreement as to the minimum amount of dietary iron required by a healthy adult. Excreted iron may never have been absorbed, it may have been absorbed, unused and later excreted or it may be unconserved hemoglobin iron and iron from the breakdown of tissue cells. The iron of various foods cannot be absorbed equally from the digestive tract, and it is not certain that all the metal absorbed is available for physiologic use. It is possible, as Heath and Patek [98] have done, to calculate the total quantity of iron required by the human body from birth throughout life, but such calculations are based on an assumption of 100 per cent conservation of breakdown iron. In the healthy adult approximately 75 mg. of iron is released daily by the disintegration of erythrocytes; if the efficiency of conservation of the metal were 90 per cent, the daily loss to be replaced by diet would be 7.5 mg. Hemorrhage or an abnormal rate of destruction of the red blood cells would, of course, increase this figure.

Leverton and Roberts [99] carried out continuous balance studies on 4 healthy young women for from three to five months. The loss of iron

97. Snapper, I.; Groen, J.; Hunter, D., and Witts, L. J.: Achlorhydria, Anaemia and Subacute Combined Degeneration in Pituitary and Gonadal Insufficiency, Quart. J. Med. **6**:195, 1937.

98. Heath, C. W., and Patek, A. J., Jr.: Anemia of Iron Deficiency, Medicine **16**:267, 1937.

99. Leverton, R. M., and Roberts, L. S.: Iron Metabolism of Normal Young Women During Consecutive Menstrual Cycles, J. Nutrition **13**:65, 1937.

by menstruation was slight, but the calculation of iron requirements gave an optimum daily allowance for a 56 Kg. woman of 16 to 17 mg. daily.

It is now common experience that for optimum regeneration of hemoglobin in patients with anemia much greater amounts of medicinal iron are required than are necessary for the synthesis of hemoglobin, and this is true regardless of the chemical state of the iron administered. The question arises as to whether the excess of iron is needed solely because of inefficient absorption or whether, after absorption, only a portion of the metal is put to physiologic use. Recent studies by a number of workers emphasize the discrepancy between retained iron and that employed in the formation of hemoglobin.

Reimann, Fritsch and Schick [100] carried out iron balance experiments on 7 patients with anemia due to iron deficiency and on 2 healthy persons. To all the subjects iron was given, usually ferrous chloride, 100 mg. daily. They detected no retention of the metal by the healthy subjects but about 50 per cent retention by the patients with anemia. Of the total iron administered to these patients, 20 per cent went into new hemoglobin, and of the iron retained, about 45 per cent was used for hemoglobin synthesis, the difference presumably effecting repletion of the iron stores. These authors concluded that a positive iron balance with retention of iron forms the basis for the therapeutic action of iron. Iron balance studies clearly differentiate anemia due to iron deficiency from other types of anemia.

A series of investigations of the retention and utilization of iron has been reported by Fowler and Barer.[101] Their earlier work paralleled in scope the studies of Reimann and his colleagues, but their results differed somewhat from those of the German workers. Ten patients with hypochromic anemia were studied during continuous six day periods with respect to the intake and excretion of iron and the formation of new hemoglobin. To each patient was given iron and ammonium citrates, 1 Gm. three times a day. They found that of the total iron administered, an average of 32.6 per cent was retained, but only about 2 per cent was used for new hemoglobin. There was no correlation between the retention and the utilization of the orally administered iron, and as much as 5.85 Gm. of the metal was retained by 1 patient. They suggested a possible deleterious effect of continued administration of large doses of iron, in that such quantities of retained metal might

100. Reimann, F.; Fritsch, F., and Schick, K.: Eisenbilanzversuche bei Gesunden und bei Anämischen: II. Untersuchungen über das Wesen der eisenempfindlichen Anämien ("Asiderosen") und der therapeutischen Wirkung des Eisens bei diesen Anämien, Ztschr. f. klin. Med. **131**:1, 1936.

101. Fowler, W. M., and Barer, A. P.: Retention and Utilization of Orally Administered Iron, Arch. Int. Med. **59**:561 (April) 1937.

lead to pigmentary cirrhosis of the liver. The discrepancy between their observations of the percentage of iron utilized for new hemoglobin and those reported by the German workers may be attributed to the much smaller doses of iron used by the latter in their studies. This view is supported by a later study of Fowler, Barer and Spielhagen,[102] in which they reported a much higher percentage of iron utilization when smaller doses were administered.

Barer and Fowler[103] studied the iron exchange of 15 patients with achlorhydria and 11 with normal or low gastric acid values in an attempt to ascertain the effect of gastric acidity on the retention of iron. The subjects were consistently in negative iron balance while receiving diets supplying less than 7 mg. of the metal daily. In the presence of achlorhydria there was diminished retention of dietary iron, but when medicinal iron was given, 500 mg. daily, the percentage of the metal retained was not affected by lack of free hydrochloric acid. The administration of hydrochloric acid to patients with achlorhydria did not increase the retention either of medicinal or of food iron. They also made the striking observation, in direct contrast to the report of Reimann and his colleagues, that the presence of anemia did not in their studies influence the amount of iron retained.

Barer and Fowler[104] investigated, by means of iron balance studies in 10 cases of hypochromic anemia, the effect of copper and liver extract supplements on the retention and utilization of iron. They found that addition of copper led to diminished retention but slightly increased utilization of iron when the latter was given in the relatively small amounts of 217 to 260 mg. daily. When 400 to 500 mg. was given the effect of copper supplements was negligible. Addition of liver extract was followed by a slightly decreased retention of iron. The rise in hemoglobin in their series was no more rapid with the addition of copper or liver extract than with iron alone.

The same authors[105] reported their experiences with iron administered parenterally. To 4 patients 0.1 Gm. of iron and ammonium citrates was given daily by intramuscular injection. The iron was retained but failed to appear in newly formed hemoglobin. From this observation they concluded that parenterally administered iron cannot

102. Fowler, W. M.; Barer, A. P., and Spielhagen, C. F.: Retention and Utilization of Small Amounts of Orally Administered Iron, Arch. Int. Med. **59**:1024 (June) 1937.

103. Barer, A. P., and Fowler, W. M.: Influence of Gastric Acidity and Degree of Anemia on Iron Retention, Arch. Int. Med. **59**:785 (May) 1937.

104. Barer, A. P., and Fowler, W. M.: Influence of Copper and a Liver Fraction on the Retention of Iron, Arch. Int. Med. **60**:474 (Sept.) 1937.

105. Fowler, W. M., and Barer, A. P.: Retention and Utilization of Parenterally Administered Iron, Arch. Int. Med. **60**:967 (Dec.) 1937.

be recovered in newly formed hemoglobin. It is not possible to accept without qualification the results of this study. Although it is difficult to conceive of a situation in which parenteral iron therapy is indicated, the high degree of utilization of injected iron for new hemoglobin has been demonstrated by numerous investigators and is in accord with our own experience. The apparently contradictory results obtained by the workers in Iowa may be due to their use of relatively small doses of iron, 12.3 mg. daily, since an optimum rate of increase of hemoglobin utilizes approximately three times this amount.

The retention of orally administered iron by persons with anemia and by those with normal blood values was studied by Brock and Hunter.[106] They found that both anemic persons and those with normal blood values retained large amounts of orally administered iron and that the retention was actually much greater than might have been inferred from the rate of increase of hemoglobin. Brock [107] also reported that only 1 of these patients with hypochromic anemia showed an increase in hemoglobin commensurate with the iron retained. Another patient had but slight improvement of anemia, although sufficient iron was retained to have caused the hemoglobin to become normal had utilization of the metal been complete. When the dosage of iron was doubled the hemoglobin value rapidly rose to normal. Evidence was presented in this communication for the greater effectiveness of an excess of iron as compared with a theoretically sufficient amount of iron. Small doses of ferrous salts, such as 0.6 Gm. daily, were not advised, since ease of absorption is not the sole factor involved. Brock advanced the supposition that relatively large amounts of iron in the intestine might facilitate the absorption of other minerals and substances necessary for hemopoiesis, perhaps by effecting a change in the bacterial flora.

The observations so far described, as well as others to be mentioned, concerning the quantitative difference between iron retained and that used for new hemoglobin serve as a reminder of earlier work of Starkenstein and Weden.[108] A decade ago they concluded that determinations of the iron stored in the liver and spleen give no indication of the true effectiveness of preparations used in the treatment of experimental anemia. They advanced the view that the more rapidly iron is stored in the liver and spleen, the less pharmacodynamic efficacy it possesses, and that active iron circulates throughout the organism for a relatively long time.

106. Brock, J. F., and Hunter, D.: Fate of Large Doses of Iron Administered by Mouth, Quart. J. Med. **6**:5, 1937.

107. Brock, J. F.: Relation Between the Hypochromic Anæmias and Iron Deficiency, Brit. M. J. **1**:314, 1937.

108. Starkenstein, E., and Weden, H.: Weitere Beiträge zur Pharmakologie und Physiologie des Eisens, Klin. Wchnschr. **7**:1220, 1928.

Studies of iron transportation were reported by Heilmeyer and Plötner.[109] Determinations were made of the iron content of the serum after parenteral and after oral administration of the metal. The normal basal level of the iron was found to be 0.19 mg. per hundred cubic centimeters, increasing to 0.24 mg. after the giving of 1 Gm. of reduced iron by month. In hypochromic anemia with achlorhydria no such increase occurred. In 1 case of anemia due to subacute hemorrhage the iron content rose from 0.03 to 0.35 mg. per hundred cubic centimeters after the ingestion of 220 mg. of ferrous iron; only a slight increase followed the intake of the same amount of ferric iron.

Moore [110] found that the normal range for plasma or serum iron is 0.05 to 0.18 mg. per hundred cubic centimeters and that the average for men is slightly higher than that for women. Moore, Doan and Arrowsmith [111] subdivided blood iron into: (1) iron in hemoglobin, (2) plasma iron, probably organic, not ionized and so not dialyzable, and (3) "easily split-off" iron, which was first described by Barkan (this is apparently associated with the red blood cells, is split off by dilute acids and bases and is an organic nonhemoglobinous form of iron). Plasma iron appeared to be transport iron; its value increased markedly even for normal persons after a single large oral dose of the metal. A temporary increase in the plasma iron content occurred in patients with hypochromic anemia during the period of absorption, but the basal level for such patients remained below that for normal persons until the anemia was wholly corrected. The authors failed to confirm Barkan's view of "easily split-off" iron as iron in transport and were unable to define its function.

Additional observations on iron metabolism have been made in the field of animal experimentation. Hart, Elvehjem and Kohler [112] found that commercial liver preparations which are effective in the treatment of pernicious anemia were, apart from their iron and copper content, wholly ineffective in the treatment of nutritional anemia in rats. On the other hand, when the amount of dietary protein was either qualitatively

109. Heilmeyer, L., and Plötner, H.: Eisenmangelzustände und ihre Behandlung, Klin. Wchnschr. **15**:1669, 1936.

110. Moore, C. V.: Studies in Iron Transportation and Metabolism: Chemical Methods and Normal Values for Plasma Iron and "Easily Split-Off" Blood Iron, J. Clin. Investigation **16**:613, 1937.

111. Moore, C. V.; Doan, C. A., and Arrowsmith, W. R.: Studies in Iron Transportation and Metabolism: The Mechanism of Iron Transportation and Its Significance in Iron Utilization in Anemic States of Varied Etiology, J. Clin. Investigation **16**:627, 1937.

112. Hart, E. B.; Elvehjem, C. A., and Kohler, G. O.: Does Liver Supply Factors in Addition to Iron and Copper for Hemoglobin Regeneration in Nutritional Anemia? J. Exper. Med. **66**:145, 1937.

or quantitatively inadequate for growth, the rate of regeneration of hemoglobin was significantly retarded in the case of young rats with nutritional anemia, even though sufficient iron and copper supplements were given.[113] Beard and Boggess[114] found that in the treatment of the nutritional anemia of the rat the weekly intraperitoneal injection of 2 mg. of colloidal iron over a period of four weeks was as effective as the daily oral administration of the same quantity of iron for three weeks. They determined the utilization for the formation of hemoglobin of orally administered iron to be 6 per cent in the case of a 42 mg. dose, divided over a period of three weeks, and 22 per cent for a 10 mg. dose over an equal period; for iron given intraperitoneally the utilization was 28 per cent for 8 mg. and 87 per cent for 2.73 mg. over a period of four weeks. Supplementing the iron with either copper or manganese had no apparent effect. Smith and Otis[115] found that regeneration of hemoglobin was more rapid in female than in male rats when they received the same amounts of medicinal or of food iron. They attributed the difference as possibly due to greater storage of iron in the females, the iron becoming available for hemoglobin formation when copper supplements are given. A sex difference in the rate of regeneration of hemoglobin was not observed after two weeks of iron and copper supplemented feedings. Mitchell and Hamilton[116] confirmed these observations but attributed the sex difference to a larger intake of the basal diet by the male rats in obedience to their greater growth impulse. It has been shown that in the case of anemic rats there is an inverse relation between the amount of milk consumed and the rate of regeneration of hemoglobin.

The stomachs were removed from 2 dogs by Fontès, Kunlin and Thivolle,[117] and the animals were subsequently maintained on a diet of rice and milk. During a period of six months progressively severe hypochromic anemia developed, which the authors attributed to achlorhydria resulting from gastrectomy.

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113. Pearson, P. B.; Elvehjem, C. A., and Hart, E. B.: The Relation of Protein to Hemoglobin Building, J. Biol. Chem. **119**:749, 1937.

114. Beard, H. H., and Boggess, T. S.: Comparison of Oral Administration Versus Intraperitoneal Injection of Colloidal Iron upon Blood Regeneration in Nutritional Anemia of the Rat, Am. J. Physiol. **118**:211, 1937.

115. Smith, M. D., and Otis, L.: Sex Variations in the Utilization of Iron by Anemic Rats, Science **85**:125, 1937.

116. Mitchell, H. H., and Hamilton, T. S.: Sex Differences in Anemic Rats, Science **85**:364, 1937.

117. Fontès, G.; Kunlin, J., and Thivolle, L.: L'anémie consecutive à la gastrectomie ne peut être qu'hypochrome, Nutrition **6**:331, 1936.

Continuing their studies of the role of amino acids in hemoglobin regeneration, Fontès and Thivolle [118] reported further observations on dogs made anemic by repeated bleeding in which, presumably, there was depletion not only of iron but of other substances required for hemopoiesis. They reported results gained from the use of a combination of tryptophan, histidine and the globinates of iron, copper and manganese as superior to those obtained from liver. Additional studies of the hypochromic anemia of dogs following gastrectomy were reported by Mettier, Kellogg and Purviance.[119] Predigested beef was not retained by the animals, and iron and ammonium citrates led to an increase in the total daily output of hemoglobin of from 0.25 to 2.03 Gm. Liver extract by injection was ineffective.

Landsberg [120] studied the reticulocyte response during induction of acute fatal hookworm infestation in dogs. He found the reticulocytosis accompanying the developing anemia identical with that occurring during induction of anemia by hemorrhage and so concluded that no evidence existed for the theory of myelotoxin inhibition in the etiology of hookworm anemia. He also found no signs of hemolysis in the dogs with hookworm anemia.

*Nutritional Anemia of Children.*—During the past year a number of studies have been reported bearing on the iron requirement during infancy and the treatment of the nutritional anemia of early childhood. Stearns and McKinley [121] studied the iron excretion of 7 infants, commencing at about the tenth day after birth. This is the period of maximum destruction of blood, and they found the lowest blood iron values between the fourth and the sixth week of life. During this period the infants remained in constant negative iron balance, with a daily loss of 1.25 mg. of the metal. They said they believed that a supplementary dietary source of iron is desirable before the sixth month. Studies of iron balance were carried out by Stearns and Stinger [122] on

118. Fontès, G., and Thivolle, L.: Trois nouveaux composés protéido-metalliques: Les globinates de fer, de cuivre et de manganèse; la thérapeutique équilibrée et totale de l'anémie secondaire; valeur comparée du foie de veau cru, Bull. Acad. de méd., Paris **116**:314, 1936.

119. Mettier, S. R.; Kellogg, F., and Purviance, K.: Studies on Hypochromic Anemia in Dogs: The Evaluation of Predigested Beef, Iron and Liver Extract on the Formation of Hemoglobin After Gastrectomy, J. Clin. Investigation **16**:107, 1937.

120. Landsberg, J. W.: Reticulocyte Response in Hookworm Anemia, Am. J. Hyg. **26**:60, 1937.

121. Stearns, G., and McKinley, J. B.: Conservation of Blood Iron During the Period of Physiological Hemoglobin Destruction in Early Infancy, J. Nutrition **13**:143, 1937.

122. Stearns, G., and Stinger, D.: Iron Retention in Infancy, J. Nutrition **13**:127, 1937.

14 healthy infants aged 7 to 54 weeks. One subject received human milk and was never in negative balance, although the amount of iron retained was small. The others were given evaporated cow's milk with various modifications of the formula. All the infants receiving cow's milk were in negative balance and lost an average of 0.05 mg. of iron daily. There was no relation between the age of the infant and the ability to retain iron. Egg yolk and spinach supplements did not increase the retention of iron. Retention was, however, markedly increased by the giving of a special iron-containing cereal or iron and ammonium citrates. There was no apparent relation between the amount of iron retained and the intake of potassium, calcium or phosphorus. They concluded that a daily intake of approximately 0.5 mg. of iron per kilogram, either as food iron or as a soluble salt, is necessary to insure retention of the metal and that ample retention is secured by a daily intake of 1 to 1.5 mg. per kilogram.

Schlutz, Morse and Oldham[123] determined the iron retention and utilization of 3 anemic infants. They found that additional iron supplied by puréed spinach was not retained by these infants; the iron of apricots, although retained to a slight extent, effected no change in the hemoglobin level. One hundred milligrams of the metal, supplied either as ferrous sulfate or as iron and ammonium citrates, led to a marked increase in the retention of iron and a rise in the hemoglobin value. The ferrous form was no more efficacious than the ferric salt. Supplementary copper, given as copper sulfate, had no effect either on iron retention or on the hemoglobin level. The iron exchange of 4 children with normal blood values and 2 with anemia was studied by Hutchison.[124] The children ranged in age from infancy to 11 years. Four day preliminary control periods were used, followed by consecutive seven day test periods. During the test periods there was wide variation in the excretion of iron, in spite of a constant intake. Ferrous sulfate was given in amounts totaling 4 to 8 Gm. weekly, supplying 0.803 to 1.607 Gm. of iron. Over variable lengths of time up to 112 days the subjects retained large amounts of iron, in some cases from three to seven times the normal total body content of the metal. In the case of the anemic children, less than 10 per cent of the retained iron was recoverable as new hemoglobin. For these children the retention of iron was not demonstrably allied with the ability to secrete hydrochloric acid. Hutchison suggested that retained iron stored in the liver cannot be used for the formation of hemoglobin and that, consequently, large

123. Schlutz, F. W.; Morse, M., and Oldham, H.: Effect of Various Supplements to the Diet on the Iron Balance of the Anemic Infant, J. Pediat. **10**:147, 1937.

124. Hutchison, J. H.: Studies on the Retention of Iron in Childhood, Arch. Dis. Childhood **12**:305, 1937.

doses of medicinal iron are necessary since only iron which overflows from the liver into the circulation can be utilized for hemoglobin synthesis. The gastric acidity of infants and young children was studied by Stewart.[125] Four groups were employed: (1) anemic subjects, (2) postanemic subjects, (3) those with other illnesses and (4) healthy children. The amount of acid secreted by the stomach was determined in response to a stimulus of 40 cc. of 7 per cent alcohol. The author found no correlation between the incidence of anemia and the degree of gastric acidity. She concluded that in the cases studied, anemia was caused solely by deficiency of nutritional iron and that achlorhydria is more likely to follow anemia than to precede it. She did, however, suggest that chronic gastritis might lead to achlorhydria and that the two conditions might together influence adversely the absorption of iron. Fullerton,[126] continuing his studies of the blood values for the poorer persons of Aberdeen, determined the hemoglobin level of 789 infants of all ages up to 23 months. His findings indicated that the iron content at birth is of great importance in determining the time of onset of anemia due to iron deficiency. However, the amount of storage iron was related primarily to the birth weight, and no significant correlation was found between the common degrees of maternal iron deficiency and the incidence of anemia in infancy. It was found that breast-fed infants were less liable to anemia than those receiving an artificial diet. Infections produced a rapid fall in the hemoglobin values of the infants studied, and even after subsidence of such infection there might be inhibition of response to treatment for a long time. In a series of 298 infants examined by Fullerton, subnormal hemoglobin levels, less than 11 Gm. per hundred cubic centimeters, were found for 87 per cent.

Elvehjem, Duckles and Mendenhall [127] concluded from the treatment of 70 anemic infants and children of preschool age that iron and copper, a combination of 0.2 Gm. of ferric pyrophosphate (supplying 0.025 Gm. of iron) and 0.004 Gm. of copper sulfate (supplying 0.001 Gm. of copper daily), caused maximum regeneration of hemoglobin with results superior to those gained from the use of the iron salt alone. Kato [128] carried out experimental and clinical studies of the effect of an iron and cobalt mixture in the treatment of nutritional anemia. To anemic

125. Stewart, A.: Gastric Acidity in Infants and Young Children Under Normal and Pathological Conditions, with Special Reference to Nutritional Anaemia, Brit. J. Child. Dis. **34**:1, 1937.

126. Fullerton, H. W.: The Iron-Deficiency Anaemia of Late Infancy, Arch. Dis. Childhood **12**:91, 1937.

127. Elvehjem, C. A.; Duckles, D., and Mendenhall, D. R.: Iron Versus Iron and Copper in the Treatment of Anemia in Infants, Am. J. Dis. Child. **53**:785 (March) 1937.

128. Kato, K.: Iron-Cobalt Treatment of Physiologic and Nutritional Anemia in Infants, J. Pediat. **11**:385, 1937.

infants he gave 0.5 Gm. of iron and ammonium citrates daily, later supplemented with 0.025 to 0.05 Gm. of cobalt daily. He concluded that the action of cobalt is probably catalytic, but the evidence presented of its actually enhancing the effect of iron in the series reported is not wholly convincing.

Mackay and Jacob [129] recommended the use of a stable solution of ferrous sulfate in the treatment of nutritional anemia of young children. Stability was increased by the addition of hypophosphorous acid to a solution of ferrous sulfate with dextrose. The dosage should be such as to supply 0.3 to 0.6 Gm. of the iron salt daily.

Ferrous chloride has been prepared in relatively stable form by dissolving it in a solution of cevitamic acid, thereby protecting it from oxidation for about three months. Glanzmann [130] and Stolleis [131] reported the efficacious use of this preparation in the treatment of a variety of anemias of early childhood. The former obtained excellent results from the use of liver, ferrous sulfate and cevitamic acid in the treatment of 1 patient with celiac disease and anemia. He concluded that the combination of ferrous iron and vitamin C is preferable to iron alone and suggested that vitamin C is related to iron metabolism in a manner analogous to the role of vitamin D in the metabolism of calcium and phosphorus.

The prophylactic value of iron therapy in infancy was emphasized by Alpert.[132] He concluded after a survey of the literature that "the role of copper, if any, is still unsettled, and that a longer period of observation and clinical trial is needed to determine whether copper is an important element in the treatment of anemia."

In the treatment of anemia due to iron deficiency, the use of copper in conjunction with iron has been repeatedly advocated in spite of the fact that earlier clinical studies which tended to demonstrate its value have, in general, been unconfirmed by subsequent investigations. Our own experience fails to substantiate the value of copper in the treatment of either the nutritional anemia of children or the hypochromic anemia of adults. In the opinion of Hahn,[133] the influence of copper

129. Mackay, H. M. M., and Jacob, L. E.: A Stable Ferrous Sulphate Mixture for the Treatment of Nutritional Anaemia in Young Children, Lancet **2**:570, 1937.

130. Glanzmann, E.: Zur Behandlung der Kinderanämien mit askorbinsaurem Eisen, Schweiz. med. Wchnschr. **67**:436, 1937.

131. Stolleis, D.: Beitrag zur Eisenbehandlung der Anämie in Säuglings und Kindesalter, Deutsche med. Wchnschr. **63**:819, 1937.

132. Alpert, G. R.: Physiological and Nutritional Anemias of Infancy, Arch. Pediat. **54**:268, 1937.

133. Hahn, P. F.: Metabolism of Iron, Medicine **16**:249, 1937.

on iron metabolism has been greatly overemphasized. He stated that from a practical point of view there is no indication for the inclusion of this element in anemia therapy.

*Hypochromic Anemia of Adults.*—There has been a revival of interest in chlorosis, a disease which has been almost forgotten or which when mentioned has been regarded as a nonspecific anemia of adolescent girls caused by excessive menstrual loss of blood and probably dependent on endocrine imbalance. Olef [134] attributed the apparent remarkable decrease in the incidence of chlorosis to three factors: (1) more accurate diagnostic methods by means of which many conditions formerly classified as chlorosis could now be proved to be pulmonary tuberculosis, bleeding from the digestive tract or, in spite of pallor, conditions associated with normal hemoglobin values; (2) improvement in general and personal hygiene, and (3) the present tendency to place conditions formerly called chlorosis in other etiologic categories. He reported 3 cases of chlorosis, 2 of them occurring in twins. The characteristics of this disorder, according to Olef, which together distinguish it from other anemias of young women, are the high incidence of gastric hypoacidity and achlorhydria, the frequent reduction of the plasma protein value without reversal of the albumin-globulin ratio, small, unusually flat red blood cells that are poor in hemoglobin and the common finding of thrombocytosis, which may be marked. Heath [135] reported 2 cases of chlorosis. He attributed the disorder to one or more abnormal factors at puberty, such as unusually rapid growth, excessive menstruation, poor dietary intake of iron and such gastrointestinal disorders as achlorhydria and prolonged diarrhea.

Schiødt [136] studied the rate of regeneration of red blood cells of 50 patients with hematemesis or melena from peptic ulcer. The patients received the Meulengracht treatment, a full diet of strained food from the first day of admission to the hospital. To exclude, so far as possible, the effects of prolonged bleeding on the determinations of the regeneration rate, the lowest blood value after admission of the patient to the hospital was taken as a starting point. The individual erythrocyte curves were remarkably straight, and all tended to meet at one point, 4,540,000 red blood cells per cubic millimeter thirty-three days after the lowest count was obtained, regardless of the starting level.

134. Olef, I.: Chlorosis, Ann. Int. Med. **10**:1654, 1937.

135. Heath, C. W.: Iron Deficiency in Girls: Chlorosis, M. Clin. North America **21**:389, 1937.

136. Schiødt, E.: Observations on Blood Regeneration in Man: I. The Rise in Erythrocytes in Patients with Hematemesis or Melena from Peptic Ulcer, Am. J. M. Sc. **193**:313, 1937.

These observations were in conformity with the author's theory of the normal rate of exchange which is expressed by the equation:

Average daily rise × Longevity of erythrocytes = Normal value — Lowest value.

Substituting values actually determined in this equation and using 4,540,000 for the normal value, the average span of life of the erythrocytes was found to be thirty-three days. Since the end point of regeneration of the subjects studied was below the accepted normal level, it may be inferred that a check took place. Such a check to the increase of erythrocytes may be explained by a decrease of production, a shortening of life of the red blood cells or an increase of destruction. The size of the check can be assumed to be about 15 per cent of the normal rate of exchange. In a subsequent article Schiødt [137] reported that age, sex and the form of hemorrhage do not affect greatly the rate of regeneration of erythrocytes. Blood transfusion altered the blood level temporarily but did not hasten regeneration. Additional evidence was presented of the superiority of the Meulengracht treatment for peptic ulcer with hemorrhage.

Idiopathic hypochromic anemia was defined by Fowler and Barer [138] as, in most cases, a chronic hemorrhagic anemia due to menstrual loss of blood and an improper absorption of iron resulting from deficient gastric secretion. In their cases no evidence was found of faulty iron metabolism. They observed that massive doses of iron produced a more rapid hemoglobin response in hypochromic anemia than is obtained when smaller amounts are employed. However, a daily dose of 1 to 3 Gm. of iron and ammonium citrates produced satisfactory results in their cases, even in the presence of achlorhydria, and led to storage of iron as well as the formation of hemoglobin. Iron by intramuscular injection was practically without effect. The syndrome of hypochromic anemia, achlorhydria and atrophic gastritis was described by Morrison, Swalm and Jackson.[139] They reported on 11 patients with anemia with a low color index; 9 of these showed complete achlorhydria after histamine stimulation and 2 had marked hypochlorhydria. Gastroscopic studies of these patients revealed various degrees of atrophic gastritis. The authors concluded that the anemia was a manifestation of a gen-

137. Schiødt, E.: Observations on Blood Regeneration in Man: II. The Influence of Sex, Age, Form of Hemorrhage, Treatment and Complications on Erythrocyte Regeneration After Hematemesis and Melena from Peptic Ulcer, Am. J. M. Sc. **193**:327, 1937.

138. Fowler, W. M., and Barer, A. P.: Etiology and Treatment of Idiopathic Hypochromic Anemia, Am. J. M. Sc. **194**:625, 1937.

139. Morrison, L. M.; Swalm, W. A., and Jackson, C. L.: Syndrome of Hypochromic Anemia, Achlorhydria and Atrophic Gastritis, J. A. M. A. **109**:108 (July 10) 1937.

eralized metabolic disorder in which atrophic gastritis played a dominating role and that absent or low free gastric acid was an important pathogenic factor.

Merklen and his associates [140] and later Manizade [59] studied the incidence of anemia following partial gastric resection for ulcer. Observations on the blood were made after varying intervals up to twelve years after operation. The former group of investigators found normal blood values in the majority of their series of 28 cases. When anemia occurred it was of mild degree and of hypochromic type. Manizade observed normal erythrocyte and hemoglobin values for 36 of 40 patients studied. The 10 per cent incidence of anemia following partial gastrectomy was attributed to secondary digestive disturbances and to possible constitutional predisposition to anemia.

The treatment of hypochromic anemia was investigated by Gram,[141] who calculated the response to therapy as the percentage of the deficit of hemoglobin gained during a ten day period. Thus if the normal value were assumed to be 14 Gm. of hemoglobin per hundred cubic centimeters, a patient with 7 Gm. would have a 50 per cent deficit, and if after ten days of treatment the hemoglobin value rose to 9 Gm., the percentage of the deficit recovered would be 28.6 per cent. This figure represented Gram's measure of therapeutic response. For optimal results he advised the use of ferrous preparations, supplying 0.3 Gm. of iron daily. His patients were treated, for the most part, with ferrous tartrate, 0.5 Gm. three times a day. Duckles, Wills and Elvehjem [142] studied the comparative value of iron alone and iron supplemented with copper in the treatment of mild anemia of college women. Iron was given as ferric pyrophosphate, supplying 25 mg. of the metal daily, copper as copper sulfate, yielding 1 mg. of copper daily. The addition of copper to iron failed to give superior results. Several iron compounds in common therapeutic use were found by Underwood [143] to contain appreciable cobalt contamination. He suggested that cobalt may possess therapeutic value and may so explain the need for massive doses of iron in the treatment of some patients with hypochromic anemia. An analogy was drawn with the New Zealand "bush-sickness" of sheep, in which there is evidence of cobalt deficiency.

140. Merklen, P.; Israël, L.; Froehlich, F., and Jacob, A.: Le sang des gastrectomisés, Nutrition **6**:337, 1936.

141. Gram, H. C.: Investigations on the Iron Treatment of Simple Anemias with Control, Acta med. Scandinav., 1936, supp. 78, p. 207.

142. Duckles, D.; Wills, L., and Elvehjem, C. A.: The Treatment of Hypochromic Anemia in College Women, J. Am. Dietet. A. **12**:537, 1937.

143. Underwood, E. J.: Cobalt Content of Iron Compounds and Its Possible Relation to the Treatment of Anemia, Proc. Soc. Exper. Biol. & Med. **36**:296, 1937.

A comprehensive résumé of the entire subject of anemia due to iron deficiency, including a series of case reports, was published by Heath and Patek.[98]

### ANEMIA OF PREGNANCY

Few significant contributions to the literature on anemia of pregnancy have appeared during the past year. A review of the subject was published by Evans,[144] who suggested the following classification of such anemia:

I. Deficiency anemias of pregnancy
   (*a*) Microcytic
      1. With normal or only temporary deficiency of gastric secretion
      2. With permanent deficiency of gastric secretion
   (*b*) Macrocytic
      1. With normal or only temporary deficiency of gastric secretion
      2. With permanent deficiency of gastric secretion

II. Anemia due to hemorrhage

III. Anemia due to sepsis

IV. Hemolytic anemia (due to the action of a hemolytic agent of unknown origin)

It may be appropriate to supplement Evans' classification by pointing out that the deficiency operating in microcytic anemia of pregnancy is primarily a lack of iron and that iron deficiency may occur in pregnancy with hypochromia but without microcytosis. Anemia of pregnancy with macrocytic deficiency may result from a lack of Castle's intrinsic or extrinsic factors, from insufficient vitamin B complex, from impairment of intestinal absorption or from inadequate intake of protein. The macrocytic anemia associated with hepatic damage, although due to defective blood formation, can hardly be said to result from deficiency, in the usual sense of the word.

The possible influence of vitamin B deficiency in causing macrocytic anemia during pregnancy was investigated by Elsom.[54] Eleven pregnant women were divided into two groups. To those in group 1, comprising 8 subjects, a diet was given which possessed the relatively low vitamin B per caloric ratio of approximately 1.66. The vitamin B requirement of the subjects, calculated according to Cowgill's formula, averaged 1.5 at the beginning of the study. The vitamin B demand increased in proportion to the gain in weight of the subjects, and since the diet was both qualitatively and quantitatively constant, the require-

144. Evans, E. H.: Anemias of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **44**:417, 1937.

ment of vitamin B exceeded the supply after about the two hundred and forty-fifth day of pregnancy. Those in group 2 received a varied diet, providing a vitamin B ratio of about 2.8. After the theoretic demand for vitamin B had exceeded the supply, the members of the first group showed clinical signs of vitamin B deficiency, including anorexia, constipation, glossitis with ulceration of the tongue, paresthesia of the extremities, impairment or loss of vibratory sense and symptoms of anemia. Studies of the blood for this group revealed macrocytic anemia, with a high color index, poikilocytosis and immature erythrocytes and leukocytes. Similar changes in the blood were not observed for the control group.

The subjects with evidence of vitamin B deficiency were given yeast by mouth or liver extract parenterally, with complete relief of all symptoms and with return to normal of the blood findings.

Napier and Das Gupta [145] carried out studies of the blood of women in India during pregnancy. He found the hemoglobin level of females in the general coolie population to be considerably below that of females of other countries, but there was no evidence of a general lowering of the hemoglobin value during pregnancy. The incidence of outspoken anemia was slightly greater during gestation, especially for the younger women and during the first pregnancy.

Mays [146] reported a case of severe macrocytic anemia of pregnancy that was of special interest because of associated marked thrombopenia with purpuric manifestations. The anemia, thrombopenia and purpura responded favorably to parenteral liver therapy. Malarial parasites were found in the blood of this patient, but the response to liver occurred independently of treatment of the malaria.

### POLYCYTHEMIA

Lee [147] emphasizes the familial element in polycythaemia vera. He said he felt that graduations of severity of the disease in certain families is against the idea of a neoplastic cause but favors a secondary response to some substance or condition, which, however, is not a recognizable form of anoxemia. Lee said he favored phenylhydrazine rather than venesection or roentgen therapy, because of its easier application to the average ambulatory patient.

145. Napier, L. E., and Das Gupta, C. R.: Haematological Studies in the Indians: VII. The Incidence and Degree of Anaemia Amongst Pregnant Females of the Coolie Population, Indian J. M. Research **24**:1159, 1937.

146. Mays, C. R.: Anemias of Pregnancy: A Review and Report of a Case of the Macrocytic Type with Purpuric Manifestations and Malaria, South. Surgeon **6**:458, 1937.

147. Lee, R. I.: A Case of Polycythemia Vera or Erythremia, M. Clin. North America **21**:369, 1937.

Mogensen [148] found that five months' treatment with gastric lavage as well as the low animal protein diet of Herzog was ineffective in producing a remission in a patient with a red blood cell count of 10,000,000 per cubic millimeter.

Bernard [149] was able to produce irritation of the bone marrow by the injection of tar into the marrow. Leukemic and polycythemic reactions developed.

In a man of 66 years with Geisböck's type of polycythemia, Decourt, Mathieu and Blaire [150] found that irradiation over the hypophysial area was ineffective. However, in seven months fifty-three irradiations over the bones and seven over the spleen caused a reduction in the red blood cell count from 9,200,000 to 5,800,000 per cubic millimeter. Apropos of this case, Léchelle [151] commented on a 24 year old woman with a hypophysial adenoma, polycythemia and acromegaly. Removal of the adenoma was followed by amelioration of the condition, suggesting a connection between the two. Decourt, Joly and Blair [152] obtained good results with teleroentgenotherapy in a woman of 54 years. After six months the red blood cell count was reduced from 7,350,000 to 4,000,000 per cubic millimeter. In the authors' opinion, the irradiation does not cause lysis or necrosis of the cells but hastens maturation and death from senility.

Lemierre, Laporte, Reilly and Laplane [153] reported the development of polycythemia (8,000,000 cells) in a 39 year old man with infection due to Bacillus perfringens of the perirectal fossa. The symptoms included icterus and nephritic complications, conditions in which one frequently finds anemia.

Josland [154] found that the addition of 1 per cent cobalt sulfate to the diet of 2 rats was followed by loss of weight and polycythemia

148. Mogensen, E.: Polycythemia Vera: Hypothesis Concerning Its Gastrogenic Pathogenesis Together with a Case in Which Treatment Consisted of Gastric Lavage and Diet, Hospitalstid. **80**:1271, 1937.

149. Bernard, J.: Polyglobulies et leucémies provoquées par les injections intramédullaires de goudron, Ann. de méd. **40**:373, 1936.

150. Decourt, J.; Mathieu, P., and Blaire, G.: Erythrémie du type Geisböck: Echec de la radiothérapie de la région infundibulo-hypophysaire, rémission sous l'influence de la radiothérapie osseuse et splénique, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:807, 1937.

151. Léchelle, P.: Polyglobulies d'origine centrale et érythrémies du type Geisböck, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:978, 1937.

152. Decourt, J.; Joly, M., and Blaire, G.: Maladie de Vaquez, traitée avec succès par la téléroentgenthérapie totale, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:812, 1937.

153. Lemierre, A.; Laporte, A.; Reilly, J., and Laplane, R.: Sur un cas d'érythrémie apparue au cours d'une infection prolongée à "Bacillus perfringens," Bull. et mém. Soc. méd. d. hôp. de Paris **53**:831, 1937.

154. Josland, S. W.: The Effect of Feeding Cobalt to Rats, New Zealand J. Scient. Tech. **18**:474, 1936.

within seven weeks. There was no cirrhosis of the liver, although much of the cobalt was stored in this organ.

Brewer [155] was not able to produce cobalt polycythemia in dogs, even with comparable doses which would have caused a 50 per cent increase in red blood cells in the rat. Cobalt chloride caused toxic necrosis of the tissues of the dog on subcutaneous injection, although this method of administration is not injurious to the rat. Davis,[156] however, found that the oral administration of 2 mg. of cobalt (as cobalt chloride) per kilogram daily to dogs produced about a 20 per cent increase in the erythrocyte value. No toxic symptoms were noted in dogs which received 6 mg. per kilogram daily for three weeks.

Cohen [157] found that the characteristic change in the fundus in polycythemia is distention and engorgement of the retinal veins, due to increase in blood volume and thinness of the venous wall. A purplish color is caused by an increase in carbon dioxide. Individual patients may show venous engorgement, edema of the disks, retinal hemorrhages, postneuritic atrophy of the optic nerve and perivascular transudation of plasma.

Vascular complications were noted in one third of the patients with polycythemia by Norman and Allen,[158] a greater incidence than that in other patients of the same age and sex. Treatment of polycythemia is advisable to prevent vascular lesions.

In the patient reported on by Schnetz [159] thromboarteritis pulmonalis developed. Clinical symptoms of acute aleukemic myelosis (agranulocytosis) were noted. In another patient with polycythemia a phlegmon of the hand developed, accompanied by mild neutropenia. Improvement was noted on administration of vitamins A and C.

Seggel,[160] in describing a case of polycythemia, noted the association of hepatic cirrhosis with polyglobulism. Ascites may suggest this lesion or thrombosis of the portal vein. In such cases the patients may also show icterus.

In a 25 year old man with alcoholic cirrhosis of the liver and ascites, polycythemia was present. There was erythrosis, absence of macro-

155. Brewer, G.: Erythrocyte Reaction of the Dog to Cobalt, Am. J. Physiol. **118**:207, 1937.

156. Davis, J. E.: Cobalt Polycythemia in the Dog, Proc. Soc. Exper. Biol. & Med. **37**:96, 1937.

157. Cohen, M.: Lesions of Fundus in Polycythemia: Report of Cases, Arch. Ophth. **17**:811 (May) 1937.

158. Norman, I. L., and Allen, E. V.: Vascular Complications of Polycythemia, Am. Heart J. **13**:257, 1937.

159. Schnetz, H.: Polycythaemia vera mit Ausgang in Agranulocytose und Thrombarteriitis pulmonalis, Folia haemat. **57**:110, 1937.

160. Seggel, K. A.: Ueber besondere Verlaufsformen der Polycythaemia vera, Ztschr. f. klin. Med. **132**:466, 1937.

cytosis and characteristics of Vaquez' disease. Relief was obtained with phenylhydrazine, and Benhamou, Fourès and Mutin [161] concluded that cirrhosis of the liver is not a contraindication to this type of therapy.

From porphyrin studies, Dobriner [162] concluded that there is increased hemopoietic activity in pernicious anemia, polycythaemia vera and Hodgkin's disease.

In none of 6 patients with polycythaemia vera were Israel and Mendell [163] able to demonstrate gonadotropic substance in the urine (Zondek method).

Sachs, Levine and Griffith [164] studied the reciprocal relation of copper and iron in the blood. The iron content of the blood for normal men was found to average 50 mg. per hundred cubic centimeters and for women 45 mg. The copper content of the blood of both was 0.132 mg. per hundred cubic centimeters. Hypercupremia was associated with hypoferronemia. In a 65 year old woman with polycythemia, the iron and copper contents of the blood were 53.16 and 0.113 mg., respectively, when the red blood cell count was 6,080,000 per cubic millimeter. On the production of anemia with phenylhydrazine (3,520,000 erythrocytes) the copper and iron contents of the blood were 39.36 and 0.2 mg., respectively. Through relapses and induced remissions the iron content paralleled the red blood cell count, while the copper content rose and fell in a reciprocal relation.

McCance and Widdowson [165] found that less than 0.5 per cent of the iron liberated by the hemolysis of the red blood cells in the acetylphenylhydrazine treatment of a patient with polycythemia was excreted. Of the nitrogen, 31 per cent was eliminated; of the potassium, 5 per cent, and of the copper, 30 per cent. After discontinuance of the medication a rapid destruction of the red blood cells followed, with a temporary rise in the blood urea content to 145 mg. per hundred cubic centimeters and with an increased excretion of urea, creatine and undetermined nitrogen.

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161. Benhamou, E.; Fourès, and Mutin L.: Cirrhose de foie avec polyglobulie traitée par la phénylhydrazine, Sang **11**:772, 1937.

162. Dobriner, K.: Porphyrin Excretion in Feces in Normal and Pathological Conditions, J. Biol. Chem. **120**:115, 1937.

163. Israel, S. L., and Mendell, T. H.: Excretion of Gonadotropic Substance in Polycythemia Vera, Endocrinology **21**:123, 1937.

164. Sachs, A.; Levine, V. E., and Griffith, W. O.: Reciprocal Relationship of Copper and Iron in the Blood: Polycythemia Vera, Proc. Soc. Exper. Biol. & Med. **35**:6, 1936.

165. McCance, R. A., and Widdowson, E. M.: The Fate of Elements Removed from Blood Stream During the Treatment of Polycythaemia by Acetylphenylhydrazine, Quart. J. Med. **6**:277, 1937.

Sgalitzer [166] advised the use of "total irradiation" in the treatment of polycythemia. The entire body is irradiated from a source at 1.5 meters (180 to 200 kilovolts on six successive days for fifteen minutes daily, alternating the ventral and the dorsal surface of the body). The leukocyte number is used as a gage of treatment. From twelve to twenty-two irradiations may be given in from four to ten weeks, depending on the sensitivity of the leukocytes. Relapses have been noted in from eighteen months to five years.

Bétroux and Marcoulidès [167] found that their patient with erythremia resisted roentgen therapy; in fact, the treatment exaggerated the symptoms. Phenylhydrazine hydrochloride, in doses of 0.05 Gm. for four days, 0.1 Gm. for four days and 0.15 Gm. for three days, gave a satisfactory hemopoietic response.

Limarzi, Keeton and Seed [88] removed the thyroid gland from a patient with polycythemia. During the course of the subsequent year there was gradual symptomatic and hemopoietic improvement.

Stephens and Kaltreider [168] studied the therapeutic use of venesection in 5 cases of polycythemia. Remissions of from eight months to two years were obtained by withdrawing 500 cc. of blood at intervals of one to three days until the red blood cell count, hemoglobin value and hematocrit percentage reached normal or slightly subnormal levels. Excellent symptomatic remissions were experienced, and no evidence of stimulation of the bone marrow (reticulocytosis) was noted.

### PURPURA HAEMORRHAGICA

Purpura may be caused by many factors, and various forms have been classified. In an attempt to clarify the complex problems associated with the multiple etiologic factors of purpura, Ainsworth [169] and Mettier and Purviance [170] have offered simple classifications. Peck, Rosenthal and Erf [171] have studied the mechanism of the production of

166. Sgalitzer, M.: Ueber Röntgen-Totalbestrahlungen bei Blutkrankheiten, Wien. klin. Wchnschr. **50**:125, 1937.

167. Bétroux, L., and Marcoulidès, J.: Erythrémie essentielle (maladie de Vaquez), peu influencée par la téléroentgenthérapie totale, rapidement améliorée par le chlorhydrate de phénylhydrazine, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1390, 1936.

168. Stephens, D. J., and Kaltreider, N. L.: The Therapeutic Use of Venesection in Polycythemia, Ann. Int. Med. **10**:1565, 1937.

169. Ainsworth, M. L.: Purpuras, Ohio State M. J. **33**:849, 1937.

170. Mettier, S. R., and Purviance, K.: Classification and Treatment of the Hemorrhagic States: Value of Roentgen Irradiation of Spleen in Essential Thrombocytopenic Purpura Haemorrhagica, J. A. M. A. **108**:83 (Jan. 9) 1937.

171. Peck, S. M.; Rosenthal, N., and Erf, L.: Purpura: Classification and Treatment, with Special Reference to Treatment with Snake Venom, Arch. Dermat. & Syph. **35**:831 (May) 1937.

purpura and have classified the disease from a dermatologic and hematologic standpoint. According to these authors, bleeding may be due to diapedesis or to rupture of the capillary wall. Increased capillary pressure, suction and reduction of intercellular tissue between the endothelial cells aid diapedesis. Rhexis of the capillary wall is caused by toxins, heavy metals, snake venom or trauma. In addition to changes in the vessels, purpura may be due to thrombopenia, essential or secondary. To determine which of these factors is the cause of purpura, Peck and his co-workers recommended the snake venom test.

Fleischhacker,[172] studying the pathogenesis of the purpuras associated with deficiency of platelets, observed that the problem could be simplified by studies of the bone marrow. The physiochemical changes of the blood associated with experimental purpura were noted by Tocantins.[173] He stated that there are a moderate decrease in the viscosity of the blood and a transient increase in the nonprotein nitrogen content. Venous pressure, the viscosity of the plasma, the specific colloid osmotic pressure and the protein content of the plasma are not altered.

Both hereditary and acquired thrombopenic purpura have been described. Posner[174] pointed out that purpura is rare in pregnancy and that even more rare is the occurrence of purpura in the fetus. Wintrobe and Hanrahan[175] concluded from their observations in a series of 62 cases that the disease is predominant in childhood or adolescence, the sex incidence is equal and the disease rarely occurs in Negroes. They added that the course is variable; acute episodes are the rule rather than the exception, and recurrences are common. Pernokis[176] reported 17 cases of symptomatic purpura and 5 cases of idiopathic purpura in a series of 2,728 cases. Purpura associated with dysmenorrhea has been noted by Smith.[177] Hazel and Snow[178] observed purpura in a patient with septicemia due to gonococcic infection. The

172. Fleischhacker, H.: Ueber Thrombopenien (Einteilung und Knochenmarksbefunde), Wien. klin. Wchnschr. **50**:1480, 1937.

173. Tocantins, L.: Physicochemical Changes of the Blood in Experimental Thrombopenic Purpura, Proc. Soc. Exper. Biol. & Med. **36**:402, 1937.

174. Posner, A. C.: Purpura Hemorrhagica Complicating Puerperium, Am. J. Obst. & Gynec. **34**:155, 1937.

175. Wintrobe, M. M.; Hanrahan, E. M., Jr., and Thomas, C. B.: Purpura Haemorrhagica, J. A. M. A. **109**:1170 (Oct. 9) 1937.

176. Pernokis, E. W.: Blood Studies: Report of 2,728 Cases, J. A. M. A. **108**:1686 (May 15) 1937.

177. Smith, E. C.: Menstrual Purpura, New Orleans M. & S. J. **90**:214, 1937.

178. Hazel, O. G., and Snow, W. B.: Gonococcic Septicemia with Purpura and Arthritis Successfully Treated by Hyperthermia, J. A. M. A. **109**:1275 (Oct. 16) 1937.

relation of purpura and lupus erythematosus was discussed by Keil,[179] who pointed out that the reduction in platelets is due to their withdrawal from the blood stream and their inclusion in the thrombi in the smaller blood vessels. Purpura due to "drug poisoning" has been observed by Kramer,[180] van Andel and Groen,[181] Schonberg,[182] Goodman and Levy [183] and Padget and Moore.[184]

Purpura associated with alterations in the permeability of the vascular membranes may be the result of allergy. Wright and Bacal [185] reported a case of allergic tuberculous purpura. Idiopathic thrombopenic purpura due to an anaphylactoid reaction was observed by Lytle and Ward.[186] Squier and Madison [187] stressed the importance of food allergy as a cause of purpura and reported 3 cases in which the etiology was proved. That allergic purpura may present a serious surgical problem was stressed by Althausen and his colleagues.[188] These authors pointed out the necessity of a carefully taken history and the value of blood studies to differentiate allergic purpura from an acute abdominal condition. They added that the use of epinephrine may also be of value for establishing a definite diagnosis.

The determination of the causal factor of purpura before the institution of treatment is most important, and since this cannot always be accomplished, failure of therapy may result. Sternal puncture [189] to determine the presence or absence of megakaryocytes should be per-

179. Keil, H.: Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, Brit. J. Dermat. **49**:221, 1937.

180. Kramer, P. H.: Purpura Haemorrhagia After the Use of Sedormid, Nederl. tijdschr. v. geneesk. **8**:3345, 1937.

181. van Andel, P., and Groen, J.: Thrombopenic Purpura (Werlhof's Disease) After Use of Sedormid, Nederl. tijdschr. v. geneesk. **81**:3348, 1937.

182. Schonberg, I. L.: Purpuric and Scarlatiniform Eruption Following Sulfanilamide, J. A. M. A. **109**:1035 (Sept. 25) 1937.

183. Goodman, M. H., and Levy, C. S.: The Development of a Cutaneous Eruption (Toxicodermatosis) During the Administration of Sulfanilamide, J. A. M. A. **109**:1009 (Sept. 25) 1937.

184. Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **60**:887 (Nov.) 1937.

185. Wright, H. P., and Bacal, H. L.: Allergic Tuberculous Purpura, Am. J. Dis. Child. **53**:1276 (May) 1937.

186. Lytle, C. C., and Ward, D. F.: Idiopathic Thrombopenic Purpura, J. Iowa M. Soc. **27**:296, 1937.

187. Squier, T. L., and Madison, F. W.: Thrombocytopenic Purpura Due to Food Allergy, J. Allergy **8**:143, 1937.

188. Althausen, T. L.; Deamer, W. C., and Kerr, W. J.: False "Acute Abdomen," Henoch's Purpura and Abdominal Allergy, Ann. Surg. **106**:242, 1937.

189. Goldhamer, S. M.: Bone Marrow Studies in Purpura, unpublished data.

formed before splenectomy is attempted. In many instances the removal of the spleen has been followed by little or no improvement. The failure of improvement may be due to the fact that the bone marrow is not producing platelets; hence splenectomy is an unnecessary procedure. Wintrobe [175] stated that splenectomy is not specific; Mettier and Purviance [170] stated the opinion that the removal of the spleen is of questionable value; Ainsworth [169] recommended this procedure.

Peck and his co-workers [171] advised the use of snake venom. Eagle [190] studied the various types of venoms and their effectiveness and noted that about 50 per cent were of value. Roentgen therapy has been employed by Mettier and Purviance with good results, but Ainsworth concluded that its value is questionable. In cases of drug poisoning and allergy the inciting factor should be removed. Hildebrandt [191] observed satisfactory results with vitamin C and iron, whereas Vervloet [192] reported the opposite. Since spontaneous remissions are not uncommon, a conservative attitude must be adopted concerning the value of the various therapeutic agents recommended.

### HEMOPHILIA

The essential clinical features of hemophilia are its inheritance, the occurrence in males, a history of repeated hemorrhages, a prolonged clotting time and a normal bleeding time. The disease is transmitted according to the mendelian laws by the female. Bauer and Meller [193] said they were not entirely in accord with this view. They carefully reviewed the literature referable to the presence of hemophilia in women and stated that there is sufficient evidence to justify the assumption that hemophilia may exist in females. In support of this conclusion they cited 4 cases.

Included in the group of diseases associated with abnormal bleeding is a syndrome known as hereditary pseudohemophilia. Fowler [194] described 2 cases of this disease. The outstanding clinical features are hereditary transmission by either sex to either sex, occurrence at any

190. Eagle, H.: Coagulation of Blood by Snake Venoms and Its Physiologic Significance, J. Exper. Med. **65**:613, 1937.

191. Hildebrandt, A.: Zur Behandlung starker Genitalblutungen bei essentieller Thrombopenie, Med. Welt **11**:1103, 1937.

192. Vervloet, C. G.: Treatment of Werlhof's Disease and Other Thrombopenic Forms of Purpura, Nederl. tijdschr. v. geneesk. **81**:3940, 1937.

193. Bauer, H., and Meller, J.: Ueber weibliche Hämophilie, Wien. klin. Wchnschr. **50**:495, 1937.

194. Fowler, W. M.: Hereditary Pseudo-Hemophilia, Am. J. M. Sc. **193**:191, 1937.

age (usually late childhood or adolescence), recurrent hemorrhages from any organ (spontaneous or traumatic), normal platelet count, prolonged bleeding time and normal clotting time.

Pachman [195] described 3 cases of hemophilia in Negroes, in 2 of which there was a definite family history. He stressed the fact that the occurrence of this disease in Negroes is rare. Placental extract was of value in 1 of 2 cases. Estrogenic substance (theelin) proved helpful in 1 instance.

The defect of the coagulation mechanism has recently received considerable attention. Bendien and van Creveld [196] isolated a substance from normal fresh serum or plasma which will promote coagulation in blood of a hemophiliac person. The investigators said they believed that this factor is absent from the blood in hemophilia. Patek and Taylor [197] and Pohle and Taylor [198] also have isolated a substance from normal plasma which promotes coagulation. A detailed method for obtaining this material is described by them. Various experiments employing the use of this product with favorable results are reported. The effect of trypsin on the clotting of blood in hemophiliac persons was studied by Tyson and West.[199] The authors concluded that trypsin accelerates coagulation of the blood in vitro and that its action is similar to that of thrombin.

In spite of the important experiments which have been performed, the specific treatment of hemophilia still remains a mystery. Some of the common agents employed are whole blood, citrated blood, human plasma, human and animal serum, defibrinated blood, hemostatic preparations, fibrinogen, cephalin, calcium, sodium citrate, protein shock, liver and its derivatives, whole ovary and ovarian extracts. Kohl [200] reported satisfactory results with histidine administered enterally and parenterally. The value of estrogenic substance has yet to be established. Pohle and

195 Pachman, D. J.: Hemophilia in Negroes, J. Pediat. **10**:809, 1937.

196. Bendien, W. M., and van Creveld, S.: Investigations on Hemophilia, Am. J. Dis. Child. **54**:713 (Oct.) 1937.

197. Patek, A. J., and Taylor, F. H. L.: Hemophilia: Some Properties of a Substance Obtained from Normal Human Plasma Effective in Accelerating the Coagulation of Hemophilic Blood, J. Clin. Investigation **16**:113, 1937.

198. Pohle, F. J., and Taylor, F. H. L.: The Coagulation Defect in Hemophilia: The Effect in Hemophilia of Intramuscular Administration of a Globulin Substance Derived from Normal Human Plasma, J. Clin. Investigation **16**:741, 1937.

199. Tyson, T. L., and West, R.: Effect of Trypsin on the Clotting of the Blood in Hemophilia, Proc. Soc. Exper. Biol. & Med. **36**:494, 1937.

200. Kohl, H.: Histidinbehandlung der Hämophilie, Ztschr. f. klin. Med. **132**:40, 1937.

Maddock [201] recommended the use of maggot therapy for infected wounds. They stated that the danger of hemorrhage is minimized and the infection is readily eliminated.

### BLOOD CLOTTING

The most extensive review concerning the necessary factors for coagulation and the mechanism involved has been published by Eagle.[202] Heilingbrunner and Schörcher [203] have pointed out that cessation of bleeding and coagulation are independent processes. Bleeding from vessels is controlled by the contraction of the vessel walls and as long as hemorrhage continues a clot cannot form. The nature of the clot has received considerable attention from McKhann and his co-workers.[204] They described it as a firm gelatinous mass with meshes of fibrin, containing variable amounts of water and some formed elements of the blood. Variations in the clot content may occur in different blood dyscrasias.

Several interesting experiments relating to coagulation of the blood have been performed. Terazawa and his colleagues [205] determined the effect of vitamin C on coagulation. They said that they believed that it accelerates the process by increasing the number of platelets and the amount of thrombin and fibrinogen. Taliaferro and Haag [206] stated that congo red in small amounts decreases the coagulation time but that large doses tend to have the opposite effect. Delayed or prolonged coagulation subsequent to anaphylactic shock was said by Eagle and his co-workers [207] to be due to an increased amount of antithrombin. Brinkhous, Smith and Warner [208] stated that the hemorrhagic disease of

201. Pohle, F. J., and Maddock, S.: Maggot Therapy in an Infected Wound in Hemophilia, J. A. M. A. **109**:2055 (Dec. 18) 1937.

202. Eagle, H.: Recent Advances in the Blood Coagulation Problem, Medicine **16**:95, 1937.

203. Heilingbrunner and Schörcher, F.: Die Blutstillung mit körpereigenem Gewebe, Deutsche Ztschr. f. Chir. **248**:475, 1937.

204. McKhann, C. F.; Chu, F. T.; Green, A. A., and Eley, R. C.: Character of the Blood Clot in Normal Persons and in Hemophiliacs, Tr. Am. Pediat. Soc. **48**:61, 1936.

205. Terazawa, N.; Takeda, K., and Mizoguchi, K.: Effect of Vitamin C on Coagulability of Rabbit Blood, Jap. J. Obst. & Gynec. **20**:550, 1937.

206. Taliaferro, M. A., and Haag, H. B.: Toxicity and Effect of Congo Red upon Blood Coagulation, Am. J. M. Sc. **193**:626, 1937.

207. Eagle, H.; Johnston, C. G., and Ravdin, I. S.: On the Prolonged Coagulation Time Subsequent to Anaphylactic Shock, Bull. Johns Hopkins Hosp. **60**:428, 1937.

208. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Plasma Prothrombin Level in Normal Infancy and in Hemorrhagic Disease of New Born, Am. J. M. Sc. **193**:475, 1937.

newborn infants is probably due to decreased amounts of prothrombin, which condition may be readily corrected with transfusions. The effects of histidine on the clot mechanism were studied by Bloch, Kosse and Necheles,[209] who concluded that it has no apparent effect. The role of calcium in clot formation was investigated by Ferguson.[210] In his opinion, calcium is probably a thrombin stabilizer.

Dam and his co-workers [211] first suggested that a certain dietary deficiency in animals produces a marked hemorrhagic tendency. The missing substance was termed vitamin K. It is fat soluble and is present in hog liver oil, cabbage, spinach, tomatoes and alfalfa. It occurs in a nonsterol fraction of unsaponifiable fat, and it closely resembles vitamin E in solubility and in resistance to heat.

Almquist [212] isolated vitamin K and described a method for concentrating it. Almquist and Stokstad [213] further demonstrated that chicks with a hemorrhagic tendency can be cured with an extract from alfalfa. The vitamin was described by Almquist as a nonnitrogenous substance with an aromatic nucleus; it does not contain phosphorus, sulfur or a sterol ring. It is alkali labile, heat stabile and optically inactive, with a molecular weight of about 600. Ultraviolet light, aluminum oxide and magnesium oxide destroy its activity.

Schönheyder [214] demonstrated that vitamin K is present in prothrombin of normal chicks but absent or inactive in chicks with hemorrhagic disease. Roderick [215] showed that a marked hemorrhagic tendency exists in animals fed spoiled sweet clover hay, and that this tendency to bleed is related to a deficiency of prothrombin. Dam,

209. Bloch, L.; Kosse, J., and Necheles, H.: Clotting Time of Blood Following Administration of Histidine, J. A. M. A. **109**:204 (July 17) 1937.

210. Ferguson, J. H.: An Intermediary Calcium Complex in Blood Coagulation, Am. J. Physiol. **119**:755, 1937.

211. Dam, H.: Haemorrhages in Chicks Reared on Artificial Diets: New Deficiency Disease, Nature, London **133**:909, 1934; Antihaemorrhagic Vitamin of the Chick: Occurrence and Chemical Nature, ibid. **135**:652, 1935; Antihaemorrhagic Vitamin of the Chick, Biochem. J. **29**:1273, 1935. Dam, H.; Schönheyder, F., and Lewis, L.: Requirement for Vitamin K of Some Different Species of Animals, ibid. **31**:22, 1937. Dam, H.; Schönheyder, F., and Tage-Hansen, E.: Studies on the Mode of Action of Vitamin K, ibid. **30**:1075, 1936.

212. Almquist, H. J.: Anti-Hemorrhagic Vitamin, Poultry Sc. **16**:166, 1937; Further Studies on the Anti-Hemorrhagic Vitamin, J. Biol. Chem. **120**:635, 1937.

213. Almquist, H. J., and Stokstad, E. L. R.: Hemorrhagic Chick Disease of Dietary Origin, J. Biol. Chem. **111**:105, 1935.

214. Schönheyder, F.: Anti-Hemorrhagic Vitamin of the Chick: Measurement and Biological Action, Nature, London **135**:653, 1935; Quantitative Determination of Vitamin K, Biochem. J. **30**:890, 1936.

215. Roderick, L. M.: Pathology of Sweet Clover Disease in Cattle, J. Am. Vet. M. A. **74**:314, 1929; A Problem in the Coagulation of the Blood: Sweet Clover Disease of Cattle, Am. J. Physiol. **96**:413, 1931.

Schönheyder and Lewis determined the requirements of vitamin K for various species of animals. In some species hemorrhagic symptoms developed rapidly with a deficient diet and responded readily to substitute treatment; in others, symptoms developed slowly and in some the deficient diet had no effect. The authors explained these differences by stating that (1) some animals may not need vitamin K; (2) others may synthesize it and (3) bacteria may produce vitamin K in the intestines of certain animals. They have never observed the disease in man and reported that vitamin K is of no value to hemophiliac persons.

The so-called vitamin T factor (fat soluble) was studied by Schiff and Hirschberger.[216] The vitamin is present in sesame oil and is not present in cod liver oil and olive oil. When administered in therapeutic amounts to children, it produced a marked increase in the number of platelets.

### BANTI'S DISEASE

An accurate appreciation of Banti's disease, as described by Banti in 1881 and 1894, may be obtained from translations[217] of his original articles. Banti stated that the course of the disease could be divided into three stages which lasted for several years. He postulated that the etiologic agent was an unidentified toxic substance that was carried to the spleen, with secondary involvement of the liver. The pathologic changes noted were sclerosis of the splenic vessels, atrophy of the malpighian corpuscles, induration of the pulp, sclerosis of the portal system and atrophic cirrhosis of the liver. The treatment was splenectomy.

The existence of this disease at present is questioned.[218] The pathologic changes, which were thought by Banti to be specific, have been shown by Thompson and his co-workers[219] to be due to increased pressure in the splenic vein, with secondary effects in the spleen. Gravano[220] also said he believed that primary splenomegaly involves the portal and splenic veins or the splenic veins alone. The former is

216. Schiff, E., and Hirschberger, C.: Ueber den T-Factor, Jahrb. f. Kinderh. **150**:247, 1937; Thrombocytosis Produced by a Hitherto Unknown Substance—"Fat-Soluble T Factor," Am. J. Dis. Child. **53**:32 (Jan., pt. 1) 1937.

217. Banti, G.: Splenomegaly with Cirrhosis of the Liver, translation, M. Classics **1**:907, 1937; Splenomegaly with Cirrhosis of the Liver, translation, ibid. **1**:913, 1937.

218. Lawrence, J. S.: Indications for Splenectomy in a Medical Practice, Internat. Clin. **2**:221, 1937.

219. Thompson, W. P.; Caughey, J. L.; Whipple, A. O., and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), J. Clin. Investigation **16**:571, 1937.

220. Gravano, L.: Esplenomegalia primitiva congestiva, Semana méd. **1**:488, 1937.

termed the diffuse intraperiphlebitic type and is toxic or infectious in nature; the latter is the cryptogenic form, and the etiologic factor is unknown.

The most commonly observed symptoms and signs, as well as the outstanding differential diagnostic features, have been reviewed by Foti.[221] Splenomegaly, weakness, hemorrhage, enlargement of the liver, jaundice and ascites are the most common findings. Fittipaldi [222] described the case of a young girl with miliary tuberculosis who presented the clinical picture of Banti's disease. He said he believed that cirrhosis of the liver may be due to chronic intoxication from tuberculous toxins from the spleen which enter the hepatic viscera through the portal system. The hematemesis which is so common was said by Serafin [223] to be the result of mechanical and pathologic changes in the spleen. He concluded that the enlargement of the spleen compresses the lienal vein and causes secondary traumatic changes in the blood vessels, with the production of aseptic thrombophlebitis. The physiopathologic factor is an increase in the pressure in the venous system, as previously mentioned.

For several years the accepted treatment for Banti's disease has been splenectomy. Serafin [223] recommended removal of the spleen early in the course of the disease. He also said that anastomosis of the portal system and the inferior vena cava may be of some value. Gravano [220] advised splenectomy for the cryptogenic form of splenomegaly but not for the diffuse intraperiphlebitic type. Serbin,[224] in discussing the presence of splenomegaly in pregnancy, stated that transfusions and splenectomy are indicated to prevent the progress of the disease. Bergeret and Caroli [225] stated that splenectomy is beneficial in selected cases only. An unusual case of splenic anemia which was benefited by splenectomy was reported by Manson-Bahr, Strauss and Ruttan.[226] In opposition to these observations, Lawrence said he doubted the existence of the disease and stated that splenectomy is of no value.

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221. Foti, A.: Clinical Consideration of Splenic Enlargement, M. Rec. **145**:60, 1937.

222. Fittipaldi, C.: Splenomegalia tubercolare con cirrosi epatica e sindromi bantiane tubercolari (contributo anatomo-patalogico), Pathologica **29**:275, 1937.

223. Serafin, P. J.: Banti's Disease with Gastrorrhagias and Thrombophlebitis, Am. J. Surg. **35**:76, 1937.

224. Serbin, W. B.: Splenomegaly in Pregnancy, Am. J. Obst. & Gynec. **34**:486, 1937.

225. Bergeret, A., and Caroli, J.: Suites éloignées de la splénectomie au cours des cirrhoses du foie, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1019, 1937.

226. Manson-Bahr, P. H.; Strauss, J. N., and Ruttan, H. R.: An Unusual Case of Splenic Anaemia Treated by Splenectomy, Lancet **2**:1518, 1936.

ERYTHROBLASTOSIS FOETALIS

In erythroblastosis foetalis Javert [227] noted that the placenta may be yellow, the vernix deep yellow, and the fluid which appears on rupture of the membranes, amber. The newborn child shows a palpable liver and spleen. In the birth of these infants it is preferable to use no anesthetic. Erythroblasts appear in the blood of the infant and in the fetal capillaries of the placenta in increased numbers. At the Woman's Clinic of New York the incidence noted in 1936 was 1 : 400 infants, but the actual incidence is probably greater.

Nittis and Spiliopulos [228] noted a similarity between erythroblastic anemia and congenital malaria both as to blood and as to skeletal changes. Seven of 8 patients with erythroblastic anemia were apparently completely relieved of all their clinical and hematologic symptoms after a maximum period of three months of quinine therapy.

Caffey [68] made a roentgen study of 21 cases of erythroblastic anemia. The earliest lesion of the skull was a thickening of the lower frontal squamosa. Radial striations developed first in the anterior portion of the parietal bones near the sagittal suture, and the frontal bone was the site of the earliest and most marked thickening. The first change in the long bones was dilatation of the medullary canals, with atrophy of the cortical and cancellous bone. Reticulation of the long bones did not appear until several months later. In 15 cases of sickle cell anemia, no significant changes were observed in the long bones, but in 10 cases there was thickening of the calvarium similar to that seen in cases of erythroblastic anemia. Vertical striations of the skull were not present, but in contrast to erythroblastic anemia, the parietal bones showed more marked involvement than the frontal bones. In 6 cases of chronic hemolytic icterus there were no significant changes in the long bones. Two of the patients showed thickening and striation of the calvarium similar to those of erythroblastic anemia, but the parietal bones were more involved than the frontal.

In this connection the observations of Wakefield, Dellinger and Camp [229] on the osseous remains of the mound builders in eastern Arkansas are of interest. Two skulls and the femurs and tibias showed characteristic changes suggesting sickle cell anemia, congenital hemolytic jaundice and erythroblastic anemia, similar to that usually found in members of the Mediterranean races.

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227. Javert, C. T.: Erythroblastosis Fetalis as a Cause of Infantile Mortality: Preliminary Report, Am. J. Obst. & Gynec. **34**:1042, 1937.

228. Nittis, S., and Spiliopulos, G.: Similarity of Erythroblastic Anemia and Chronic or Congenital Malaria: Successful Treatment of Eight Patients with Quinine, Am. J. Dis. Child. **54**:60 (July) 1937.

229. Wakefield, E. G.; Dellinger, S. C., and Camp, J. D.: A Study of the Osseous Remains of the "Mound Builders" of Eastern Arkansas, Am. J. M. Sc. **193**:488, 1937.

SICKLE CELL ANEMIA

Robinson [230] found that red blood corpuscles aspirated from the sternum of a patient with sickle cell anemia showed the same tendency to sickle as blood from other regions.

Cardozo [231] found that both the blood grouping and the distribution of immune agglutinogens M and N did not differ materially in patients showing sickling from those of normal persons. In Chicago the incidence of sickling was 9.42 per cent in Negroes and 0.32 per cent in non-Negroes. The average incidence given in other available reports was 7.44 per cent. No specific agglutinogens could be demonstrated. Serum was not necessary for the sickling of the erythrocytes, and the tendency remained in the cell, no matter how long it was preserved, provided the cell itself remained intact.

Diggs, Pulliam and King [232] studied 39 cases of sickle cell anemia roentgenologically and were able to study the bones at necropsy in 8 cases. The primary involvement was in the marrow. The factor of hyperplasia of the marrow as well as osteoporosis was present. Sclerosis was most marked in the long bones (see also the reference to Caffey in the section on erythroblastic anemia).

The cardiac complications were emphasized in the case reported by King and Janeway.[233] Johnson and Townsend [234] summarized their experiences in 30 cases, and Dale [235] reported additional data.

Lewis' [236] patient was pregnant and had a history of three abortions at four to seven months. The author suggested sickle cell anemia as an etiologic agent in habitual abortion. However, the patient reported on by Sodeman and Burch [237] had an uneventful delivery of an infant which subsequently showed sicklemia.

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230. Robinson, H. A.: Sickle Cell Anemia; Bone Marrow Studies, J. Michigan M. Soc. **36**:964, 1937.

231. Cardozo, W. W.: Immunologic Studies of Sickle Cell Anemia, Arch. Int. Med. **60**:623 (Oct.) 1937.

232. Diggs, L. W.; Pulliam, H. N., and King, J. C.: Bone Changes in Sickle Cell Anemia, South. M. J. **30**:249, 1937.

233. King, J. T., Jr., and Janeway, C. A.: Sickle Cell Anemia with Cardiac Complications, Internat. Clin. **3**:41, 1937.

234. Johnson, F. B., and Townsend, E. W.: Sickle Cell Anemia: Report of Thirty Cases, South. Med. & Surg. **99**:377, 1937.

235. Dale, G. C.: Sickle Cell Anemia, South. Med. & Surg. **99**:14, 1937.

236. Lewis, A. W., Jr.: Sickle Cell Anemia with Pregnancy, Am. J. Obst. & Gynec. **33**:667, 1937.

237. Sodeman, W. A., and Burch, G. E.: Pregnancy in Active Sickle Cell Anemia, New Orleans M. & S. J. **90**:156, 1937.

Harden [238] pointed out the "hair-on-end" appearance in roentgenograms of the skulls of patients with long-standing sickle cell anemia. There was marked tortuosity of the retinal blood vessels in his patient, a 9 year old Negro. The superficial temporal vessels were also extremely tortuous and thickened.

Haden and Evans [239] reported the occurrence of sickle cell anemia in 2 patients of Sicilian ancestry, in whom no known Negro admixture existed. There was definite symptomatic improvement after splenectomy, although mild hemolytic anemia persisted. The authors said they considered that splenectomy has some value in this disease.

Hansen-Prüss [240] found that by supravital staining with brilliant cresyl blue or janus green the maximum sickling phenomenon of susceptible red blood cells could be elicited in from four to five hours instead of twenty or more hours by the method of unstained moist preparation. With this technic, 14 per cent of an unselected group of 100 Negroes showed the trait, as contrasted with the reported average of 6 per cent with the older methods.

### INFECTIOUS MONONUCLEOSIS

The etiology of infectious mononucleosis is unknown. Various organisms have been isolated and described as the causative factor, but none of the work has been confirmed. Nyfeldt [241] recently studied the etiology of this disease and found that the group of Listerellae were pathogenic for both men and animals.

The clinical features of the disease and the various procedures necessary for the establishment of the diagnosis have been summarized by Durupt.[242] Recognition of the condition is most important because of its resemblance to the hemocytoblastomas, which have a fatal prognosis. Israëls [243] pointed out the similarity of infectious mononucleosis and monocytic leukemia but stated that the differences in the blood picture and the sheep cell agglutination reaction should aid in the differential

238. Harden, A. S., Jr.: Sickle Cell Anemia: Changes in Vessels and in Bones, Am. J. Dis. Child. **54**:1045 (Nov.) 1937.

239. Haden, R. L., and Evans, F. D.: Sickle Cell Anemia in the White Race: Improvement in Two Cases Following Splenectomy, Arch. Int. Med. **60**:133 (July) 1937.

240. Hansen-Prüss, O. C.: Experimental Studies of Sickling of Red Blood Cells, J. Lab. & Clin. Med. **22**:311, 1936.

241. Nyfeldt, A.: Studies on the Etiology of Infectious Mononucleosis, Hygiea **99**:433, 1937.

242. Durupt, A.: Le diagnostic sérologique des mononucléoses infectieuses, Presse méd. **45**:1219, 1937.

243. Israëls, M. C. G.: Infectious Mononucleosis (Glandular Fever) and Monocytic Leukemia, Brit. M. J. **1**:601, 1937.

diagnosis. Ustvedt [244] stressed the difficulties encountered in differentiating infectious mononucleosis from acute myeloblastic leukemia. He suggested the use of sternal puncture as a means of establishing the diagnosis.

Since Paul and Bunnell devised an agglutination test which appears to be practically specific for infectious mononucleosis, many investigators have substantiated their work. A careful serologic study of 30 cases of infectious mononucleosis was made by Davidsohn.[245] His study was based on a modified technic which he devised. In his opinion the differential test is most important for: (1) confirmation of the diagnosis of infectious mononucleosis in cases in which there is a definite clinical and hematologic picture; (2) exclusion of cases in which the condition simulates infectious mononucleosis, with similar blood findings; (3) establishment of the diagnosis in cases in which the blood pictures is atypical, and (4) aid in the recognition of cases of late infectious mononucleosis and cases in which the condition is complicated by injections of serum.

### AGRANULOCYTOSIS

Since the original description of agranulocytic angina by Schultz, in 1922, the disease has been firmly established as a clinical entity. Multiple etiologic factors have been recognized, but the mechanism involved in the production of the syndrome is still obscure. Schattenberg [246] stated that the leukopoietic disorder may result from endocrine disturbances, radiation, infection, allergy or the toxic effect of drugs. To this list may be added protein shock.

The drug most commonly indicted as a cause of agranulocytosis is aminopyrine. Davis and Frissell [247] gave aminopyrine daily to 32 patients for varying periods up to three months without demonstrating any alteration in the white blood cell count. They also observed patients who had used the drug for more than four years without dangerous clinical symptoms. Of 50 patients who received cutaneous tests with aminopyrine, only 1, who was sensitive to the drug, reacted positively. Davis and Frissell also reported 20 cases of agranulocytosis, 9 in patients who were known to have taken aminopyrine and 1 after the ingestion of antipyrine methylaminomethane sodium sulfonate.

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244. Ustvedt, H. J.: Infectious Mononucleosis, Norsk mag. f. lægevidensk. **98**:139, 1937.

245. Davidsohn, I.: Serologic Diagnosis of Infectious Mononucleosis, J. A. M. A. **108**:289 (Jan. 23) 1937.

246. Schattenberg, H. J.: Present Day Conception of Agranulocytic Angina, New Orleans M. & S. J. **90**:78, 1937.

247. Davis, J. S., and Frissell, L. F.: Amidopyrine Hypersensitivity, J. Lab. & Clin. Med. **23**:107, 1937.

Magee [248] cited 3 cases of agranulocytosis. The use of aminopyrine was definitely established in 2. Shapiro and his associates [249] observed a man in whom agranulocytosis developed after he had taken cinchophen, 0.5 Gm. three times daily for about three weeks. They pointed out that cinchophen (phenylquinoline carboxylic acid) under certain conditions may yield benzene or nitrophenol, either of which can cause a paralyzing effect on the bone marrow. A fatal case of agranulocytosis due to intramuscular injections of a bismuth preparation was reported by Dowds,[250] who specifically stated that aminopyrine was not a contributing factor. Embleton [251] reported a case of rhythmic neutropenia in a middle-aged woman. The cause was not determined. Agranulocytosis associated with purpura and tuberculous laryngitis was noted by Taylor.[252] The neutropenia followed the administration of a gold compound. Das Gupta and Witts [253] observed a case of agranulocytosis with a characteristic bone marrow picture after the administration of gold. The possibility of aminopyrine intoxication was considered, but no changes in the peripheral blood were observed with test doses. Agranulocytosis due to sulfanilamide poisoning was reported by Young [254] and by Jennings and Southwell-Sander.[255]

Several theories have been advanced in an attempt to explain the mechanism of agranulocytosis. Fitz-Hugh [256] stated that the theory of "maturation arrest" cannot account for the sudden disappearance of granulocytes from the peripheral blood. A more likely explanation, he concluded, of the "shock mechanism" of this phenomenon is the adhesion of the leukocytes to the capillary endothelium. Holten [257] offered the hypothesis that the bone marrow reaction is an Arthus phenomenon

248. Magee, C. G.: Agranulocytosis, Practitioner **139**:185, 1937.

249. Shapiro, S., and Lehman, L.: A Case of Agranulocytosis Following Ingestion of Cinchophen, Am. J. M. Sc. **192**:705, 1936.

250. Dowds, J. H.: Agranulocytic Angina Following Bismuth Injections in a Case of Syphilis, Brit. M. J. **2**:620, 1937.

251. Embleton, D.: Rhythmical Neutropenia with Recurrent Buccal Ulceration, Proc. Roy. Soc. Med. **30**:980, 1937.

252. Taylor, A. B.: Agranulocytic Angina, Purpura and Tuberculous Laryngitis Complicating Pulmonary Tuberculosis, with Recovery, Lancet **2**:73, 1937.

253. Das Gupta, C. R., and Witts, L. J.: Chronic Agranulocytosis Successfully Treated with Liver, Brit. M. J. **1**:1197, 1937.

254. Young, C. J.: Agranulocytosis and Para-Amino-Benzene Sulphonamide, Brit. M. J. **2**:105, 1937.

255. Jennings, G. H., and Southwell-Sander, G.: Anemia and Agranulocytosis During Sulfanilamide Therapy, Lancet **2**:898, 1937.

256. Fitz-Hugh, T., Jr.: Etiology and Pathology of Agranulocytic Angina: Present Day Findings and Hypotheses, Am. J. Clin. Path. **7**:524, 1937.

257. Holten, C.: Considerations and Experiments on Hypersensitive Nature of Amidopyrine Agranulocytosis, Am. J. M. Sc. **194**:229, 1937.

localized to the leukopoietic part of the marrow. He failed to demonstrate passive transfer of aminopyrine sensitivity, nor was he able to show cutaneous sensitivity in a patient who was hypersensitive to the drug when administered orally. Golden and Silverglade [258] attempted to produce agranulocytosis in guinea pigs by sensitizing them with a benzene compound but were unable to demonstrate any changes in the leukocyte count.

Davis and Frissell [247] summarized the literature regarding aminopyrine hypersensitivity and found discussions of three theories to explain the role of aminopyrine intoxication in the production of granulocytopenia: 1. All drugs with the benzene nucleus, or the benzene nucleus in association with an amino group, are per se toxic, presumably to the bone marrow. 2. Aminopyrine is semispecific for the bone marrow and produces a direct intoxication of the leukopoietic tissue. 3. The hemopoietic changes are the result of an allergic reaction. In addition to the various theories suggested, none of which is adequate in all instances, it should be emphasized that fatigue, infection, age and menstruation play an important part in the production of the disease.

The pathologic changes occurring in agranulocytosis are distinct. The bone marrow shows a maturation arrest at the myeloblast-myelocyte stage;[259] few, if any, of the myeloid cells migrate into the peripheral blood. Ulcerations of the mucous membranes are characterized by tissue necrosis without a neutrophil inflammatory reaction and are subject to secondary invasion by bacteria. Recovery is initiated by leukopoietic hyperplasia of the marrow, a myelocyte crisis in the peripheral blood, monocytosis, the normal production of polymorphonuclear leukocytes and elimination of the infection in the tissues.

In the treatment of agranulocytosis, drugs which may play a part in the etiology of the disease should, of course, be withdrawn. Repeated small transfusions are frequently indicated. Intramuscular injections of pentnucleotide solution or of liver extract are often valuable. Marberg and Wiles [260] stressed the efficacy of yellow bone marrow.

### BLOOD CHANGES FROM SULFANILAMIDE AND RELATED COMPOUNDS

With the increasing use of sulfanilamide and related compounds in certain bacterial infections, many reports on changes in the blood have appeared. Harvey and Janeway [70b] described 3 cases of a rapidly devel-

258. Golden, A., and Silverglade, A.: Sensitization of Guinea Pigs to Cyclic Compounds and Effect on the Hematopoietic System, Proc. Soc. Exper. Biol. & Med. **37**:400, 1937.

259. Beckman, H.: Pharmacological Analysis of Agranulocytosis, Tr. Am. Therap. Soc. **36**:41, 1936. Schattenberg.[246] Fitz-Hugh.[256]

260. Marberg, C. M., and Wiles, H. O.: Yellow Bone Marrow Extracts in Granulocytopenia: Preliminary Report, J. A. M. A. **109**:1965 (Dec. 11) 1937.

oping hemolytic anemia characterized by leukocytosis and immature red and white blood cells in the peripheral circulation. Recovery followed cessation of the administration of the drug and the giving of blood transfusions. A striking resemblance to the hemolytic crisis produced by the use of phenylhydrazine was noted. The reaction is an individual response to the drug. Later 8 more cases of this type were noted (Bohlman [261]), hemoglobinuria being noted in 1 case.

Long and Bliss [262] noted 7 cases in which hemolytic anemia developed, characterized by a sudden fall in the hemoglobin value and red blood cell count and the appearance of macrocytosis, anisocytosis, poikilocytosis, leukocytosis, normoblastosis and reticulocytosis. Of the 7 patients, 6 were jaundiced, and all showed urobilinuria. All the patients recovered, 5 of them after one or more blood transfusions. In another patient neutropenia developed, but test doses did not elicit a similar response after recovery, showing a difference from aminopyrine sensitivity in this respect. One of Carey's [263] 38 patients showed a fall in the red blood cell count from 5,000,000 to 2,000,000 per cubic millimeter during ten days (52 Gm. of sulfanilamide). In McQuarrie's [264] case hemolytic anemia developed after four days of therapy, and transfusions were ineffective in saving the patient's life. In these cases there appeared to be no close correlation between the dosage of the drug and the development of anemia. Kohn's [70a] patient, a 1 year old child, showed hemoglobinuria, leukocytosis and immature red and white blood cells. Recovery was rapid. Common features in sulfanilamide anemia were fever and evidence of intense illness.

Numerous reports of extreme neutropenia following sulfanilamide therapy, frequently fatal, have appeared (Bernstein; [265] Borst; [266] Jennings and Southwell-Sander; [255] Massell; [267] McIntosh, Wilcox and

261. Bohlman, H. R.: The Use of Sulphanilamide, Dis. of Chest **3**:24, 1937.

262. Long, P. H., and Bliss, E. A.: The Clinical Use of Sulphanilamide and Its Derivatives in the Treatment of Infectious Diseases, Ann. Int. Med. **11**:575, 1937.

263. Carey, B. W., Jr.: The Use of Para-Aminobenzenesulphonamide and Its Derivatives in the Treatment of Infections Due to the Beta Streptococcus Hemolyticus, the Meningococcus and the Gonococcus: Report of Thirty-Eight Cases, J. Pediat. **11**:202, 1937.

264. McQuarrie, I.: Report on Cases Treated with Sulphanilamide (Prontosil and Prontylin), J. Pediat. **11**:188, 1937.

265. Bernstein, S. S.: Report on the Use of Sulphanilamide at the Children's Hospital of Michigan, J. Pediat. **11**:198, 1937.

266. Borst, J. G. G.: Death from Agranulocytosis After Treatment with Prontosil Flavum, Lancet **1**:1519, 1937.

267. Massell, B. F.: Studies on the Use of Prontylin in Rheumatic Fever, New England J. Med. **216**:487, 1937.

Wright;[268] McQuarrie;[264] Mitchell and Trachsler;[269] Model;[270] Plumer;[271] Trumper,[272] and Young[254]).

In some patients cyanosis has developed, with methemoglobinemia and sulfhemoglobinemia (Archer and Discombe,[273] Bensley and Ross,[274] Daniels,[275] Discombe,[276] Frost,[277] Kane,[278] Paton and Eaton[279] and Stoness.[280] These substances have been demonstrated in the blood of patients. Marshall and Walzl[281] suggested that the dark color may be due to a product of the drug itself.

### HODGKIN'S DISEASE AND LYMPHOSARCOMA

Medlar, Hornbaker and Ordway[282] presented additional data supporting the theory of Hodgkin's disease as a neoplasm of megakaryocytes. In the blood of patients with Hodgkin's disease many monocytes are atypical, and it is possible that these are really young megakaryocytes.

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268. McIntosh, R.; Wilcox, D. A., and Wright, F. H.: Results of Sulphanilamide Treatment at the Babies' Hospital, New York City, J. Pediat. **11**:167, 1937.

269. Mitchell, A. G., and Trachsler, W. H.: Report on the Use of Sulphanilamide and Its Derivatives at the Children's Hospital, Cincinnati, J. Pediat. **11**:183, 1937.

270. Model, A.: Agranulocytosis and Para-Aminobenzenesulphonamide, Brit. M. J. **2**:295, 1937.

271. Plumer, H. E.: Neutropenia Occurring During the Use of Prontylin, New England J. Med. **216**:711, 1937.

272. Trumper, A.: Prontylin and Prontosil, New England J. Med. **216**:857, 1937.

273. Archer, H. E., and Discombe, G.: Sulphaemoglobinaemia: Its Cause and Prevention, Lancet **2**:432, 1937.

274. Bensley, E. H., and Ross, J. B.: Methaemoglobinemia Due to Sulphanilamide, Canada M. A. J. **37**:62, 1937.

275. Daniels, A. P.: Case of Sulphaemoglobinaemia Due to the Simultaneous Use of Magnesium Sulphate and Sulphanilamide, Nederl. tijdschr. v. geneesk. **81**:1837, 1937.

276. Discombe, G.: Sulphaemoglobinaemia Following Sulphanilamide Treatment, Lancet **1**:626, 1937.

277. Frost, L. D. B.: Sulphaemoglobinaemia Following Antistreptococcal Chemotherapy, Lancet **1**:5110, 1937.

278. Kane, F. F.: Case of Sulphaemoglobinaemia Following Administration of Drugs of Sulphonamide Group, Ulster M. J. **6**:144, 1937.

279. Paton, J. P. J., and Eaton, J. C.: Sulphaemoglobinaemia and Methaemoglobinaemia Following the Administration of P-Aminobenzenesulphonamide, Lancet **1**:1159, 1937.

280. Stoness, J. F.: Methemoglobinemia and Prontylin, New York State J. Med. **37**:1139, 1937.

281. Marshall, E. K., and Walzl, E.: On the Cyanosis from Sulphanilamide, Bull. Johns Hopkins Hosp. **61**:140, 1937.

282. Medlar, E. M.; Hornbaker, J. H., and Ordway, W. H.: Interpretation of the Nature of Hodgkin's Disease: Further Studies, Folia haemat. **57**:52, 1937.

Jackson [283] proposed a classification for Hodgkin's disease and allied disorders. The classification, on a cytologic basis, is as follows: (1) lymphocytoma, lymphosarcoma, lymphatic leukemia, diffuse intraglandular hypertrophy of lymphoid tissue; (2) reticulum cell sarcoma, early Hodgkin's disease, Hodgkin's disease and Hodgkin's sarcoma. The members of this group are considered as varying manifestations of the same neoplastic tendency. The maximum duration of Hodgkin's sarcoma is rarely more than three years; that of Hodgkin's disease, ten years; that of lymphosarcoma, rarely three years and never ten years; that of reticulum cell sarcoma, rarely ten years, but with appropriate treatment, ten to fifteen years.

In the report of the Metropolitan Life Insurance Company [51] for the years 1921 to 1935, it is stated that 1,877 persons died of Hodgkin's disease, an incidence of 0.9 per cent. There were 950 white males, 104 Negroes, 732 white females and 91 Negresses. The death rate per hundred thousand was 0.8.

Bacaloglu and Enachesco [284] studied the problem of abdominal Hodgkin's disease. Undulating fever lasting about a week, with gastrointestinal symptoms, diarrhea alternating with constipation, anemia, splenomegaly, leukopenia with relative neutrophilia, eosinopenia and variable monocytosis characterize the disease.

Roentgen therapy is advocated. Leukopenia marked Boyer's [285] case, the leukocyte count fluctuating between 900 and 4,200 per cubic millimeter. A Pel-Ebstein type of fever was present. Peripheral lymphadenopathy was negligible. Typical abdominal Hodgkin's disease was evident at autopsy. Cutaneous ulcers, resulting from breakdown of nodules or of the skin over Hodgkin's growths, were studied by Senear and Caro.[286] The ulcers may be mistaken for those of syphilis, sarcoma, mycosis, fungoides, epithelioma and tuberculosis. Pain is variable and occasionally is severe. Usually the lesions are punched out, with elevated margins. The ulcers are deep, and the underlying tissue may be involved extensively; the necrotic tissue may give rise to a fetid odor.

Jackson [287] concluded that roentgen therapy does not, on the average, prolong life in Hodgkin's disease, but persistent treatment, especially

283. Jackson, H., Jr.: Classification and Prognosis of Hodgkin's Disease and Allied Disorders, Surg., Gynec. & Obst. **64**:465, 1937.

284. Bacaloglu, C., and Enachesco, M.: La lymphogranulomatose abdominale maligne, Presse méd. **45**:76, 1937.

285. Boyer, S., Jr.: Hodgkin's Disease with Leukopenia, J. A. M. A. **108**:876 (March 13) 1937.

286. Senear, F. E., and Caro, M. R.: Ulcerative Hodgkin's Disease of Skin, Arch. Dermat. & Syph. **35**:114 (Jan.) 1937.

287. Jackson, H., Jr.: Notes on the Treatment and Prognosis of Hodgkin's Disease and Allied Disorders, M. Clin. North America **21**:361, 1937.

when combined with blood transfusions and the use of viosterol in large amounts, can produce lasting benefits even in extreme cases. When Hodgkin's disease or reticulum cell sarcoma is localized in an early stage, radical measures offer hope for a permanent cure.

Frimann-Dahl [288] gave an average of three years as the life expectancy for a patient with malignant lymphogranulomatosis. He found that roentgen treatment prolongs the life of the patient, the effects being more marked the earlier in the disease the treatment is given. With recurrence, irradiation becomes less effective.

Baensch [289] advised small initial doses (150 roentgens) in the treatment of lymphogranuloma. After this, heliotherapy is advised. During the second stage of treatment, 300 roentgens is given over each field. The fever and glandular enlargements decrease four to six days after irradiation. Radium treatment is effective only when the lesions are superficial.

In the 20 year old patient of Loeper, Lemaire and Varay,[290] tuberculosis flared up when the lymphogranuloma was irradiated.

Ducuing, Marques and Miletzky [291] found that "total roentgen therapy" was not without danger (effect on the blood). In Porta's [292] case severe herpes developed after roentgen therapy.

Hodgkin's disease at some time in its course may be fairly localized; numerous case reports present this aspect. Gordon [293] described a case in which the ocular symptoms were marked. In Lebowich's [294] case the bladder was involved. Cavazzani [295] noted gross invasion of the pharynx, nasal fossae and paranasal sinuses. Cutaneous lesions were

288. Frimann-Dahl, J.: Roentgen Treatment of Malignant Granulomatosis, Norsk mag. f. lægevidensk. **97**:1273, 1936.

289. Baensch, W.: Zur Strahlenbehandlung der Lymphogranulomatose, Med. Welt **11**:464, 1937.

290. Loeper, M.; Lemaire, A., and Varay, A.: Maladie de Hodgkin vraisemblable à localisation médiastino-pulmonaire et osseuse; tuberculose terminale, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:374, 1937.

291. Ducuing, J.; Marques, P., and Miletzky, O.: Radiothérapie totale dans les maladies des organes hématopoïétiques; modifications sanguines et déductions pratiques, J. de radiol. et d'électrol. **21**:250, 1937.

292. Porta, R.: Erpete-zoster nella linfogranulomatosi sotto-posta a radioterapia, Quaderni radiol. **1**:237, 1937.

293. Gordon, H.: Benign Lymphogranulomatosis with Ocular Symptoms, Proc. Roy. Soc. Med. **30**:1057, 1937.

294. Lebowich, J.: Hodgkin's Disease Involving Bladder: Report of Case, Am. J. Cancer **30**:758, 1937.

295. Cavazzani, F.: Linfogranuloma della faringe, delle fosse nasali e dei seni paranasali, Valsalva **13**:205, 1937.

noted in the cases reported by Cottini,[296] Nanta and Gadrat,[297] Cerutti [298] and Resl.[299] In Cabot case 23331 [300] there was generalized involvement.

Abdominal Hodgkin's disease often presents difficulties in diagnosis. Cases were described by Caselli,[301] Carnot and Lafitte,[302] Goldfarb [303] (gastro-intestinal tract), Atakam [304] (ileocecal region), Iacobovici and Stoia [305] (stomach) and Lincke [306] (small intestine). Redish [307] noted Hodgkin's disease of the stomach, peripancreatic lymph nodes, spleen and anterior wall of the chest in a man aged 54 years. The symptoms consisted of a progressively enlarging mass on the anterior thoracic wall and gaseous eructations for eight months. The blood was not abnormal. Death followed an acute massive gastric hemorrhage. Redish's case is the twenty-third of this type recorded in which the diagnosis was confirmed at autopsy.

The various localizations, with consequent protean symptoms of Hodgkin's disease, have been well illustrated by Middleton.[308] Among his patients, from 6 to 84 years of age, outstanding symptoms in individual cases were pruritis, ulceration of a lesion with a draining sinus, involvement of the breast, neuritis, herpes zoster, osseous involvement, splenomegaly, hepatopathy, retroperitoneal lymphadenopathy, medias-

296. Cottini, G. B.: Sul quadro cutaneo e glandulare in un caso di linfogranuloma maligno varieta inguinale, Arch. ital. di demat., sif. **13**:644, 1937.

297. Nanta, A., and Gadrat, J.: Sur un granulome éosinophilique cutané, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1470, 1937.

298. Cerutti, P.: Les manifestations cutanées dans la granulomatose maligne de Paltauf-Sternberg, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1454, 1937.

299. Resl, V.: Difficult Diagnosis in a Case of Lymphogranulomatosis Cutis, Česká dermat. **17**:128, 1937.

300. Generalized Lymphoblastoma, Hodgkin's Type, Cabot Case 23331, New England J. Med. **217**:322, 1937.

301. Caselli, E. G.: Linfogranulomatosis a localización abdominal en la infancia, Rev. Asoc. méd. argent. **50**:302, 1937.

302. Carnot, P., and Lafitte, A.: La forme hépato-splénique de la maladie de Hodgkin, Paris méd. **1**:447, 1937.

303. Goldfarb, S. J.: Hodgkin's Disease of Gastro-Intestinal Tract, J. Mt. Sinai Hosp. **4**:298, 1937.

304. Atakam, A. M.: Lymphogranulomatosis of the Ileocecal Region, Anadolu klin. **5**:25, 1937.

305. Iacobovici, I., and Stoia, I.: Considérations sur un cas de lymphogranulomatose maligne primitive de l'estomac, Bull. Assoc. franç. p. l'étude du cancer **26**:348, 1937.

306. Lincke, J.: Ueber isolierte Lymphogranulomatose des Dünndarmes, Zentralbl. f. allg. Path. u. path. Anat. **68**:85, 1937.

307. Redish, J.: Hodgkin's Disease of the Stomach with Fatal Gastric Hemorrhage, Arch. Path. **23**:844 (June) 1937.

308. Middleton, W. S.: Some Clinical Caprices of Hodgkin's Disease, Ann. Int. Med. **11**:448, 1937.

tinal lymphadenopathy, involvement of the lung and pleura, constitutional manifestations (general weakness, symptoms of focal infection, tuberculosis, undulant fever and alternating pyrexia), anemia, polymorphonuclear leukocytosis, leukopenia and concurrent tuberculosis.

Diagnosis by means of lymph node puncture was used by Estrada;[309] Vendeuvre, Ingelrans and Nigoul,[310] and Weil.[311] Barasciutti[312] found sternal puncture of slight value. Wurm[313] and van Rooyen[314] studied the Gordon test clinically but did not note absolute specificity. Turner and Jackson[315] found that eosinophils of normal persons produced a positive reaction to the Gordon test in animals and that the test showed a positive reaction in Hodgkin's disease in proportion to the number of eosinophils present. The authors suggested that the agent which produces paralysis is derived from the eosinophils.

Stalker, Schlotthauer and Feldman[316] noted a lesion in a dog which showed the gross and microscopic characteristics of Hodgkin's disease. This is apparently rare in animals.

Lützow-Holm[317] and Mannucci[318] speculated on the relation of Hodgkin's disease and tuberculosis. The former found no connection between the two. Müller[319] was able to trace the origin, or at least the discovery of the disease, to trauma.

Lymphosarcoma may also give symptoms because of localization or predominance of the growth in one region. In the case reported

309. Estrada, A.: La citopuntura ganglionare nella linfogranulomatosi maligna del punto di vista diagnostico, Haematologica **18**:499, 1937.

310. Vendeuvre, A.; Ingelrans, P., and Nigoul: A propos du diagnostic de la maladie de Hodgkin par la ponction ganglionaire, Echo méd. du Nord **8**:358, 1937.

311. Weil, P. E.: Diagnosis of Hodgkin's Disease by Puncture of Lymph Nodes, Nord. med. tidskr. **14**:1262, 1937.

312. Barasciutti, A.: Sulla scarsa utilità della sternopunctura come mezzo diagnostico nel granuloma maligno, Diag. e tec. di lab. **8**:481, 1937.

313. Wurm, K.: Ueber den Gordon-Test bei Lymphogranulomatose und seine praktische Bedeutung, Deutsches Arch. f. klin. Med. **181**:90, 1937.

314. van Rooyen, C. E.: Interpretation and Significance of Gordon's Test in Diagnosis of Hodgkin's Disease: A Study of One Hundred Cases, Edinburgh M. J. **44**:455, 1937.

315. Turner, J. C., and Jackson, H., Jr.: The Etiological Relationship of the Eosinophile to the Gordon Test for Hodgkin's Disease, J. Clin. Investigation **16**:657, 1937.

316. Stalker, L. K.; Schlotthauer, C. F., and Feldman, W. H.: Probable Hodgkin's Disease in a Dog: Report of a Case, Am. J. Cancer **28**:595, 1936.

317. Lützow-Holm, G.: Investigations on the Etiology of Lymphogranulomatosis, Especially the Relation Between Lymphogranulomatosis and Tuberculosis, Norsk mag. f. lægevidensk. **98**:695, 1937.

318. Mannucci, P.: Granuloma maligno e tuberculosi, Bollettino **11**:235, 1937.

319. Müller, K.: Lymphogranulomatose und Trauma, Med. Welt **11**:852, 1937.

by Cruchet and Dupin [320] there was abdominal involvement, with jaundice; in Venable's [321] case the condition was primary in the stomach; gastrointestinal perforation of the neoplasm marked Davis' [322] case; Leveuf and Godard [323] noted involvement of the small intestine in a child; in Cabot case 23111 [324] the ileum was involved; in the case reported by Brodin, Lardennois and Tédesco [325] the jejunum was involved; in the 4 cases reported by Collins and Carmody [326] there was gastric involvement, and in the case reported by Keys and Walther [327] the condition simulated duodenal ulcer. Zaph, Olin and Kirshbaum [328] have reviewed the clinical and roentgenologic aspects of lymphosarcoma of the stomach.

Reifenstein [329] described 2 patients, a man of 42 and a woman of 53 years, in whom looseness of the stools was a feature. Lymphosarcoma was demonstrated in both cases at autopsy. There was roentgen evidence of abnormality in the first case but not in the second. In the man the main involvement was in the stomach, but in the woman the duodenum, jejunum and ileum were involved. In a case described by Golub,[330] massive lymphosarcoma of the stomach with ulceration was demonstrated at autopsy. The symptoms in this case (a man aged 45 years) were those of the symptom complex of duodenal ulcer with negligible loss of weight and indefinite roentgenologic signs.

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320. Cruchet, R., and Dupin: Lymphosarcomatose abdominale avec ictère, J. de méd. de Bordeaux **114**:168, 1937.

321. Venable, D. R.: Primary Lymphosarcoma of Stomach, with Report of a Case, Texas State J. Med. **33**:327, 1937.

322. Davis, E.: Lymphosarcoma with Perforation of Gastric and Intestinal New Growth, Brit. M. J. **2**:64, 1937.

323. Leveuf, J., and Godard, H.: Les sarcomes cavitaires de l'intestin grêle chez l'enfant, Ann. d'anat. path. **18**:1067, 1936.

324. Lymphosarcoma of the Ileum, Cabot Case 23111, New England J. Med. **216**:471, 1937.

325. Brodin, P.; Lardennois, G., and Tédesco, B.: Lymphosarcome du jéjunum, Arch. d. mal. de l'app. digestif **27**:447, 1937.

326. Collins, E. M., and Carmody, M. G.: Lymphosarcoma of Stomach: Study of Four Cases, Am. J. Digest. Dis. & Nutrition **3**:884, 1937.

327. Keys, S., and Walther, W. W.: Lymphosarcoma Simulating Duodenal Ulcer, Lancet **1**:1169, 1937.

328. Zaph, S. D.; Olin, H. A., and Kirshbaum, J. D.: Lymphosarcoma of Stomach: Clinical and Roentgenological Aspects; Review of Recent Literature; Report of a Case, Am. J. Surg. **36**:476, 1937.

329. Reifenstein, E. C.: Lymphosarcoma of the Gastrointestinal Tract, Rev. Gastroenterol. **4**:82, 1937.

330. Golub, M.: Lymphosarcoma of the Stomach with Pain-Food-Ease Rhythm of Three Months Duration, Rev. Gastroenterol. **4**:228, 1937

Hirsch [331] described a primary lymphosarcoma of the liver in a man aged 32 years. The clinical symptoms were severe secondary anemia and slight jaundice. The leukocyte count ranged from 6,900 to 9,850 per cubic millimeter, with 51 to 61 per cent lymphocytes. The lymphosarcoma cells infiltrated the walls of large and small branches of the portal vein, with mural thrombi and emboli. Extensive metastases to the bone marrow replaced the normal hemopoietic tissue (myelophthisic anemia). The only other report of a similar case which Hirsch found in the literature was that by Carl Sternberg in 1934.

The genital tract was the seat of involvement in several cases, as follows: the ovary (Durfee, Clark and Peers [332]), the vulva and clitoris (Taussig [333]) and the ovary and uterus (Fornero [334]). In Squires' [335] case the cutaneous manifestation was the outstanding feature; in Judson's [336] case the breast was chiefly involved, in Métivier's [337] case the eyelid and in Cabot case 23091 [338] the retroperitoneal lymph nodes.

### LEUKEMIA

*Classification; Incidence.*—Forkner [339] presented a classification of leukemia (leukosis or leukocythemia) which included the following groups: neutrophilocytic leukemia, eosinophilocytic leukemia, basophilocytic leukemia, chloroleukemia, erythroleukemia, megakaryocytic leukemia, lymphocytic leukemia, leukosarcoma, stem cell leukemia, plasma cell leukemia and monocytic leukemia.

In the report of the Metropolitan Life Insurance Company [51] for the period from 1921 to 1935, it was stated that there were 4,333 deaths from leukemia, 0.21 per cent of the total number of deaths, constituting 1.8 per hundred thousand. The rate for white men (per hundred thousand deaths) was 2; for white women, 1.7; for Negroes, 1.3, and for Negresses, 1.1.

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331. Hirsch, E. F.: Primary Lymphosarcoma of the Liver with Metastases to the Marrow and Secondary Anemia, Arch. Path. **23**:674 (May) 1937.

332. Durfee, H. A.; Clark, B. F., and Peers, J. H.: Primary Lymphosarcoma of the Ovary: Report of a Case, Am. J. Cancer **30**:567, 1937.

333. Taussig, F. J.: Sarcoma of Vulva, Am. J. Obst. & Gynec. **33**:1017, 1937.

334. Fornero, A.: Su di una linfosarcomatosi genito-intestinale, a svilluppo simultaneo (ovaie-utero-intestino), Arch. ital. di anat. e istol. pat. **7**:419, 1936.

335. Squires, J. B.: Case of Lymphosarcoma Cutis, J. Med. **18**:194, 1937.

336. Judson, H. A.: Simultaneous Lymphosarcomatosis and Carcinoma of the Breast in the Same Individual: Case Report, Radiology **29**:578, 1937.

337. Métivier, V. M.: Lymphosarcoma of the Eyelid, Brit. J. Ophth. **21**:202, 1937.

338. Retroperitoneal Lymphosarcoma, Cabot Case 23091, New England J. Med. **216**:389, 1937.

339. Forkner, C. E.: Classification and Terminology of Leukemia and Allied Disorders, Arch. Int. Med. **60**:582 (Oct.) 1937.

Saxl [340] observed leukemia in 5 nurslings. One patient showed signs of anemia and subleukemia practically from birth; others were 6 weeks, 4½ months and 8 months old (showing chloroma, "leukemic myelocytoma or lymphocytoma"). Two had syphilitic mothers. One of these infants, as well as a boy aged 10, died of ileus caused by the leukemic infiltration. Temporary improvement of symptoms with roentgen treatment was obtained in 1 case.

*Etiologic Factors.*—Weil and Bousser [341] have analyzed 38 cases of leukemia and traumatism. In some cases leukemia was first noted after the trauma. In these cases, the past history was important in suggesting preexistence of the disease. On the other hand, trauma may aggravate or accelerate the leukemic process, or the hemorrhagic tendency may be an important factor. This must be kept in mind when surgical intervention is indicated. It is not possible to demonstrate absolutely a causative relation between leukemia and trauma. This is often a medicolegal problem. It is important, of course, to know the exact status of the patient before the accident, the chronologic relation, the duration of the interval before the leukemia develops and the character and the variety of the leukemia.

Sabrazès and Bideau [342] reported the case of a machinist aged 20 years who was exposed to oil for three years. He had myelogenous leukemia, with splenomegaly and slight lymphadenopathy. A causative relation between benzene-containing oils and the leukemia was suggested by the authors.

Acute fatal myeloblastic anemia was noted in a woman aged 55 by Adelheim [343] after malarial treatment of dementia paralytica. While the author said he believed that the malaria caused the leukemia and the exacerbation of the splenomegaly, it is possible that the disease may have been present before the treatment was begun.

*Familial and Hereditary Aspects.*—From a study of the pedigrees of 33 patients, Ardashnikov [344] concluded that leukemia is not contagious but that hereditary factors may play a part. The type of inheritance, especially in lymphatic leukemia, is a conditionally dominant autosomal type, with phenotype variation due to other genes or environ-

340. Saxl, O.: Zur Frage der Leukämie im Säuglingsalter, Jahrb. f. Kinderh. **150**:228, 1937.

341. Weil, P. E., and Bousser, J.: Leucémie et traumatisme, Ann. de méd. **40**:222, 1936.

342. Sabrazès, J., and Bideau, J., cited in Chronic Myelogenous Leukemia in Machinery Oilers, Foreign Letter (Paris), J.A.M.A. **109**:1376 (Oct. 23) 1937.

343. Adelheim, R.: Akute Myeloblastenleukämie nach Impfmalaria bei progressiver Paralyse, München. med. Wchnschr. **84**:889, 1937.

344. Ardashnikov, S. N.: Genetics of Leukæmia in Man, J. Hyg. **37**:286, 1937.

mental factors. A relation between myelogenous and lymphatic leukemia is postulated from the occurrence of these diseases in different members of a family.

Other aspects of the familial and hereditary features have been analyzed by MacDowell [345] in mice and by Morawitz [346] and Wüllenweber.[347] Kellett [348] noted acute leukemia in 1 of identical twins.

*Symptomatology and Course.*—Olmer and Boudouresques [349] concluded that the fever in leukemia arises either from infection or from metabolic disturbance. They said that the changes in both acute and chronic leukemia are of degree and represent an expression of the same process.

Penati [350] described a form of acute leukemia in which a complete remission develops, followed by recurrence within six to eight months. The initial period is characterized by hyperchromic anemia, thrombopenia, leukopenia, agranulocytosis and the presence of immature cells.

Levy, Grand and Krakauer [351] reported on a patient who presented the difficult problem of the coincidental occurrence of lymphatic leukemia and pertussis. Persistent hyperleukocytosis in pertussis suggests follow-up studies for the possibility of leukemia.

The effect of infection (bronchopneumonia) was studied in 4 cases of leukemia by Dreyfuss.[352] The reaction depended on the degree of differentiation of the leukemic cells, with abscesses in 1 case containing polymorphonuclears, and proliferating cells of leukemia and histiocytes in the 3 others. The mesenchyma of the lung is frequently involved, with growth around the vessels, bronchi, nodules and alveolar septums. Histiocytic alveolitis may be present.

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345. MacDowell, E. C.: Genetics of Mouse Leukemia, Cancer Probl., Symposium, 1937, p. 42; J. Hered. **28**:131, 1937.

346. Morawitz, P.: Erblichkeit, Rassenhygiene und Bevölkerungspolitik: Erbliche und konstitutionelle Faktoren bei einigen Blutkrankheiten, München. med. Wchnschr. **83**:2073, 1936.

347: Wüllenweber, G.: Ueber familiäre Leukämie, Deutsche med. Wchnschr. **63**:488, 1937.

348. Kellett, C. E.: Acute Myeloid Leukæmia in One of Identical Twins, Arch. Dis. Childhood **12**:239, 1937.

349. Olmer, J., and Boudouresques, J.: La fièvre dans la leucémie myéloïde; les formes intermédiares entre la leucémie myéloïde et la leucémie aiguë, Ann. de med. **41**:265, 1937.

350. Penati, F.: Leucemie acute e subacute con prestadio amielico e remissione, Minerva med. **1**:627, 1937.

351. Levy, W.; Grand, M. J. H., and Krakauer, S. A.: Lymphatic Leucemia with Pertussis, J. Pediat. **10**:781, 1937.

352. Dreyfuss, M.: Le reazioni infiammatorie dei leucemici in base allo studio della broncopolmonite in leucemia, Gior. di clin. med. **18**:965, 1937.

Cases of leukemia during the course of pregnancy have been described by Brandstrup,[353] Pontoni,[354] Mehta[355] and Zanela.[356] Mention has been made of such special features as gastric involvement (Temlin[357]), mammary changes (Haram[358]), changes in the cardiac valves (Köberle[359]) and auricular involvement (Kindler[360]) and involvement of the cardiovascular system and brain (Tedeschi[361]).

Connor[362] reported osseous changes in 2 cases of lymphatic leukemia in children. In the first case (an aleukemic lymphatic type) there was involvement of all the bones of the arms, legs, many ribs, skull and pelvis. In the second case the bones of the extremities showed the most abnormality. The roentgenographic changes consisted of rarefying processes in the medulla and cortex and lifting of the periosteum, with new bone formation of a fine lace-work type. There was irregular mottling of the skull, pelvis, femurs, tibias and fibulas, with reduplication of the cortices. A line of transparent tissue, evident between the true cortex and the newly formed bone, indicated infiltration of the soft tissue.

Osseous lesions were also described by Lukowski and Gelman[363] and by Munk and Nauta.[364]

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353. Brandstrup, E.: Leukaemia in Pregnancy, Acta obst. et gynec. Scandinav. **17**:284, 1937.

354. Pontoni, L.: Reazione mieloide in corso di gravidanza, Minerva med. **1**:415, 1937.

355. Mehta, C.: Case of Acute Lymphatic Leukemia in Pregnancy, J. Obst. & Gynaec. Brit. Emp. **44**:328, 1937.

356. Zanela, S.: Myelosis leucaemica und Chloromyelosis leucaemica in graviditate: Beitrag zur Frage der Leukämie und Schwangerschaft, Zentralbl. f. Gynäk. **61**:763, 1937.

357. Temlin, H.: Ueber Beteiligung des Magens bei leukämischen und aleukämischen Erkrankungen, Wien. klin. Wchnschr. **50**:1268, 1937.

358. Haram, B. J.: Lymphatic Leukaemia with Bilateral Mammary Changes, Lancet **1**:1277, 1937.

359. Köberle, F.: Ueber leukämische Infiltrate in den Herzklappen, Ztschr. f. Kreislaufforsch. **29**:785, 1937.

360. Kindler, W.: Ohrmuschelerkrankung und Leukämie, Ztschr. f. Hals-, Nasen- u. Ohrenh. **41**:427, 1937.

361. Tedeschi, C.: Appunti per la istologia patologica delle leucemie, Boll. d. Soc. med.-chir. di Modena **35**:373, 1935.

362. Connor, C. L.: Clinically Demonstrable Bone Changes in Leukemia, Am. J. Cancer **29**:20, 1937.

363. Lukowski, L., and Gelman, G.: Case of Acute Lymphatic Leukemia with Paradoxical Blood Picture and Extensive Changes in Bones in Child Twelve Years Old, Polska gaz. lek. **16**:724, 1937.

364. Munk, J., and Nauta, J. H.: Acute Lymphatic Leukemia with Skeletal Changes, Maandschr. v. kindergeneesk. **6**:407, 1937.

Renal complications were noted by Procházka and Vacek,[365] and prostatic symptoms were described by Jacobi, Panoff and Herzlich.[366]

Leukemia or a leukemoid blood picture is occasionally noted in neoplastic conditions such as carcinoma of the breast (Sala and Stein [367]) or of the larynx (Denoyer [368]) or with other forms of carcinoma (Penzold [369]).

Tumor formation during the course of leukemia may be the outstanding feature and may lead to an erroneous diagnosis of medullary carcinoma or of neoplasm of the breast, as in the cases described by Fleischhacker and Seyfried.[370]

In von Bonsdorff's [371] case of atypical leukosis there were multiple tumor-like growths. Held and Kieve [372] described a patient with retrobulbar and uterine leukemic masses. The disease ran an aleukemic course, with 8,800 leukocytes per cubic millimeter, 19 per cent of which were monocytoid myeloblasts.

*Involvement of the Central Nervous System.*—Changes in the central nervous system in leukemia were noted by Gordin [373] to include hemorrhages, leukemic changes in the blood vessels and infiltration with specific leukemic tissue. A fourth condition, myelomalacia due to pressure from an epidural tumor, was noted in 1 of his cases. Leukemic changes in the meninges, cranial nerves and spinal roots were present in some cases. The simultaneous existence of leukemia and glioma was noted in 1 case.

Scheinker [374] noted leukemic infiltrations in the root bundles and spinal ganglions of a patient dying of lymphatic leukemia. These

365. Procházka, F., and Vacek, V.: Case of Myelogenous Leukemia with Infiltration of Kidney, Časop. lék. česk. **76**:1413, 1937.

366. Jacobi, M.; Panoff, C. E., and Herzlich, J.: Leukemic Infiltration of Prostate, J. Urol. **38**:494, 1937.

367. Sala, A. M., and Stein, R. J.: Carcinoma of the Breast with a Condition of Blood Simulating Chronic Lymphatic Leukemia, Arch. Path. **23**:531 (April) 1937.

368. Denoyer, A.: Carcinoma laringeo in leucemico, Ann. di laring., otol. **36**:185, 1936.

369. Penzold, H.: Leukämie und Carcinom, Deutsches Arch. f. klin. Med. **180**:430, 1937.

370. Fleischhacker, H., and Seyfried, H.: Ueber Leukämien mit tumorartigem Wachstum, Wien. Arch. f. inn. Med. **30**:177, 1937.

371. von Bonsdorff, B.: Ein Fall von atypischer Leukose mit multiplen, tumorähnlichen Wucherungen, Folia haemat. **56**:426, 1937.

372. Held, E., and Kieve, P.: Leucémie myéloïde aiguë avec "tumeurs" retrobulbaire et cervicale, Helvet. med. acta **4**:371, 1937.

373. Gordin, R.: Changes in the Central Nervous System in Leukosis, Finska läk.-sällsk. handl. **79**:889, 1936.

374. Scheinker, I.: Zur Pathogenese des Herpes zoster bei lymphatischer Leukämie, Wien. klin. Wchnschr. **50**:1065, 1937.

changes were suggested as a cause of the hemorrhagic herpes present during the course of the disease.

Reviewing the literature on neurologic changes in leukemia, Minkenhof [375] added another case of subacute lymphatic leukemia which simulated meningococcic sepsis with meningitis.

*Cutaneous Manifestations in Leukemia.*—The cutaneous manifestations of leukemia have received attention from numerous authors. In addition to those cited, features of the cutaneous lesions have been described by Lapière and Compère; [376] Weil; [377] Pautrier; [378] Hitch and Smith; [379] Gattwinkel; [380] Kwiatkowski; [381] Babonneix and Gisselbrecht; [382] Scheinker; [374] Lutz; [383] Nekám; [384] Florentin and Picard; [385] Gottron; [386] Nomland; [387] Sirota and Kuznets,[388] and Brau.[389]

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375. Minkenhof, J. E.: Meningism in Leukemia and in Weil's Disease, Nederl. tijdschr. v. geneesk. **81**:4448, 1937.

376. Lapière, S., and Compère: Leucémie aiguë à cellules indifférenciées, accompagnée de leucémides cutanées spécifiques mais éphémères, à type de roséole papuleuse, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1269, 1937.

377. Weil, P. E.: Manifestations cutanées des leucémies et des granulomatoses, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1209, 1937.

378. Pautrier, L. M.: Erythrodermie quasi généralisée, mais respectant des ilots de peau saine, avec petites tumeurs à formule histologique de mycosis fungoïde, et s'accompagnant de lésions sanguines du type leucémie lymphoïde (leucocytose à 120,000 et 85 per cent de lymphocytes), Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1307, 1937.

379. Hitch, J. M., and Smith, D. C.: Lymphatic Leukemia: Report of a Case Apparently Limited to the Skin, Superficial Lymphatic Glands and Blood Stream, Arch. Dermat. & Syph. **36**:1 (July) 1937.

380. Gattwinkel: Leukämie der Haut und Erythrodermie, Arch. f. Dermat. u. Syph. **175**:578, 1937.

381. Kwiatkowski, E. L.: Sur un cas de lymphadénose cutanée "latente" accompagnée de lésions atrophiques et dyschromiques de la peau du membre supérieur gauche, d'origine spinale, probablement leucémique, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1217, 1937.

382. Babonneix, L., and Gisselbrecht: Sur un cas de leucémie lymphoïde avec leucémides, Gaz. d. hôp. **110**:816, 1937.

383. Lutz, W.: Erythrodermie exfoliante généralisée, primaire, idiopathique, évoluant ultérieurement en érythrodermie leucémique (la peau comme lieu d'origine de la leucémie), Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1230, 1937.

384. Nekám, L.: Les manifestations cutanées de la leucémie myéloïde, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1236, 1937.

385. Florentin, G. J., and Picard, D.: La forme hémorrhagique de la myélose aleucémique mégacaryocytaire, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1061, 1937.

386. Gottron, H.: Zur Leukämie der Haut, Med. Klin. **33**:373 and 404, 1937.

Epstein and MacEachern [390] found exfoliative erythroderma in 66.6 per cent of the patients with Hodgkin's disease with cutaneous manifestation. With progress of the disease, the skin became hyperpigmented and inelastic. In the group of cases of lymphoblastoma associated with leukemia the following types of cutaneous lesions were noted: (*a*) specific lesions, (*b*) toxic manifestations (lymphoblastomids or leukemids) and (*c*) accidentally associated lesions. Metastatic nodules of lymphosarcoma and shotty nodules of the face and upper extremities of myelogenous leukemia are characteristic.

Ferreira Marques [391] described the case of a man aged 76 with chronic lymphatic leukemia who had herpes zoster involving the whole trunk. In only 3 of 42 cases of leukemia with herpes zoster reported in the literature was there the myelogenous type. The maximum incidence was found to be during the second and the third year of the disease and during the age decade between 50 and 60. The disease was most frequent in males. Two cases of facial paralysis and 2 of paralysis of the extremities were noted. Ferreira Marques said he felt that the leukemic herpes zoster is a virus manifestation.

In 3 cases of lymphomatosis with cutaneous manifestations, reported by Gaté and Cuilleret,[392] the leukemic nature was shown by blood examination, biopsy and clinically (lymphadenopathy, splenomegaly and hepatomegaly).

The cutaneous lesions in monocytic leukemia were emphasized also by Sannicandro.[393] The infiltrations were of metastatic origin, with no evidence of the involvement of the local reticuloendothelial system. The lesions include nodules, macular infiltration and cutaneous hemorrhages. This patient, a man of 37, showed enlargement of the liver, spleen and peripheral lymph nodes.

Montgomery and Watkins [394] described 5 cases of monocytic leukemia with cutaneous manifestations. These varied from discrete necrotic

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387. Nomland, R.: Skin Changes in Leukemia, J. Iowa M. Soc. **27**:25, 1937.

388. Sirota, L. S., and Kuznets, M.: Pour la clinique et l'histologie de la leucémie lymphatique, Ann. de dermat. et syph. **7**:1113, 1936.

389. Brau, J. G.: Myeloid Leukemia Manifested by Skin Infiltration, Dallas M. J. **22**:121, 1936.

390. Epstein, E., and MacEachern, K.: Dermatologic Manifestations of the Lymphoblastoma-Leukemia Group, Arch. Int. Med. **60**:867 (Nov.) 1937.

391. Marques, J. F.: Herpes zoster generalisatus bei Leukämie, Arch. f. Dermat. u. Syph. **176**:295, 1937.

392. Gaté, J., and Cuilleret, P.: A propos des manifestations cutanées des leucémies, J. de méd. de Lyon **18**:299, 1937.

393. Sannicandro, G.: Le manifestazioni cutanee della leucemia monocitica, Arch. ital. di dermat., sif. **13**:263, 1937.

394. Montgomery, H., and Watkins, C. H.: Monocytic Leukemia: Cutaneous Manifestations of the Naegeli and Schilling Types; Hemocytologic Differentiation, Arch. Int. Med. **60**:51 (July) 1937.

nodules or purpuric lesions to generalized exfoliative dermatitis. Two types of monocytic leukemia are differentiated—the Naegeli type (myelogenous leukemia with a predominance of monocytes) and the Schilling type (leukemic reticuloendotheliosis). In the latter type there is a distinctive histopathologic picture, evident also on direct examination of the skin. The authors concluded that myelogenous leukemia may terminate in monocytic leukemia or that the lymphatic type may change to the monocytic type. There may be acute, chronic and aleukemic forms of the Schilling type. Temporary regression of the lesions may be produced with roentgen rays and local applications (pruritis or secondary infections), or arsenic or fever therapy may be tried.

*Leukemia and Tuberculosis.*—In the case reported by Ryan and Medlar,[395] advanced tuberculosis and lymphatic leukemia were present. Although a high lymphocyte count is usually considered of advantage in tuberculosis, the authors concluded that leukemic lymphocytes are abnormal in function.

Lukeš,[396] noting the occasional favorable influence of intercurrent infections on the course of chronic myelogenous leukemia, injected 0.1 mg. of Calmette vaccine intravenously. There were a decrease in the leukocyte count and a fall in the number of primitive cells.

Mills and Townsend [397] reported 2 cases of acute generalized tuberculosis, the blood resembling that of patients with acute myeloblastic leukemia. At autopsy the tissues were not typical of those in leukemia, however, and it was suggested that the condition may have been due to the tuberculosis.

In sensitized tuberculous rabbits, Feldman and Stasney [398] reproduced the leukemoid blood picture sometimes noted in tuberculous patients, by the injection of tuberculin. Leukocyte counts (granulocytes) of 9,000 to 48,000 rose to 42,000 to 124,000 per cubic millimeter in from twenty-four to seventy-two hours. There was marked bone marrow activity (hyperplasia and increased mitosis), but the monocytes and lymphocytes did not take part in the reaction. This leukemoid response was not elicited in nontuberculous rabbits.

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395. Ryan, W. J., and Medlar, E. M.: Coexistence of Lymphocytic Leukaemia and Far-Advanced Pulmonary Tuberculosis: Report of Case, Am. Rev. Tuberc. **36**:212, 1937.

396. Lukeš, J.: Myéloleucémie chronique et tuberculose, Časop. lék. česk. **75**:478, 1936.

397. Mills, E. S., and Townsend, S. R.: Leukaemoid Blood Picture in Tuberculosis, Canad. M. A. J. **37**:56, 1937.

398. Feldman, W. H., and Stasney, J.: Leukemoid Response of Tuberculous Rabbits to the Administration of Tuberculin, Am. J. M. Sc. **193**:28, 1937.

*Differential Diagnosis.*—To differentiate acute leukemia in certain cases from infectious mononucleosis, Ustvedt [244] noted that the characteristic myeloblastic transformation of the bone marrow is easily demonstrable on sternal puncture. In infectious mononucleosis there are fewer cells, and they are of the more normal types.

While the anemia, acute symptoms and gross immaturity of the cells help to differentiate acute leukemia from infectious mononucleosis, Israëls [243] noted that the diagnosis in some cases is more difficult. The pyrexia, splenomegaly and lymphadenopathy may be similar. In 1 case of infectious mononucleosis, hemorrhage and anemia were present. While the total leukocyte count is not necessarily characteristic, the structure of the cells and the heterophile antibody test are of value.

Abt [399] summarized the conditions in childhood which may simulate leukemia. Of those conditions in which leukocytosis is present, he listed pertussis, pneumonia, sepsis, von Jaksch's pseudoleukemic anemia, Cooley's Mediterranean erythroblastic anemia, infectious mononucleosis, mediastinal tumor and essential lipoid histiocytosis of Niemann and Pick. Among the nonleukemic conditions are sepsis, agranulocytosis, Gaucher's disease, nonlipoid splenohepatomegaly (Letterer-Siwe disease) and malaria. On the other hand, leukemia, with leukocytosis, may simulate mediastinal tumor, rheumatism, diarrhea and parotitis. In the aleukemic states the disease may simulate sepsis, appendicitis and aplastic anemia.

*Leukemoid Blood Pictures.*—A leukemoid blood picture (21,000 leukocytes, with 40 per cent myelocytes and metamyelocytes; normoblasts) was noted in a woman with subchronic arthritis by Tötterman.[400] No change, as would be expected in leukemia, appeared during two years of observation, and the material obtained on sternal puncture was interpreted as showing a nonleukemic state. A similar leukemoid picture was noted in a man with anemia due to Bothriocephalus after pneumonia. The immature leukocytes disappeared from the peripheral blood after treatment of the anemia.

Two patients with fibrosis of the bone marrow, studied by Mettier and Rusk,[401] showed a blood picture simulating that of leukemia. The first patient showed a hemorrhagic tendency and leukopenia, with moderate splenomegaly, while the other had characteristic symptoms of

399. Abt, A. F.: Diagnosis of Leukemia in Childhood, M. Clin. North America **21**:89, 1937.

400. Tötterman, G.: On So-Called Myeloid Reaction, Finska läk.-sällsk. handl. **79**:880, 1936.

401. Mettier, S. R., and Rusk, G. Y.: Fibrosis of the Bone Marrow (Myelofibrosis) Associated with a Leukemoid Blood Picture: Report of Two Cases, Am. J. Path. **13**:377, 1937.

leukemia. The medullary cavities of the bones showed increased fibrosis and a few spicules of bone, with partial obliteration of the hemopoietic tissue. No erythrogenic tissue was found in the sinusoids of the liver or spleen. The blood of 1 patient suggested the diagnosis of aleukemic myelosis with terminal leukocytosis (myelocytes, 54 per cent), whereas that of the second showed 68,500 leukocytes per cubic millimeter, with 19 per cent myelocytes and 1 per cent blasts. A few days before death occurred examination showed 62 per cent myeloblasts after much roentgen therapy.

*Types.*—A case of aleukemic plasma cell leukemia in a 66 year old woman was reported by Reiter and Freeman.[402] Symptoms included weakness, a tingling sensation in the fingers and difficulty in walking, simulating the symptoms of pernicious anemia. Although no plasma cells were reported in the peripheral blood, the tissues, especially of the liver and spleen, showed extensive infiltration at autopsy. No tumor was noted. Both plasmoblasts and plasmocytes were present.

Ten male and 5 female patients with lymphosarcoma cell leukemia were described by Isaacs.[403] The lymphosarcoma cell, present in from 4 to 98 per cent, is characterized by a large nucleolus, which in films stained with Wright's stain and brilliant cresyl blue is surrounded by a deeply staining wall of chromatin. The leukemic phase is ushered in with an exacerbation of symptoms and fever. Leukocytosis (23,000 to 156,000 cells per cubic millimeter) may be present, with progressive anemia and thrombopenia. Relapses and remissions are noted. The average duration of the leukemic phase is less than two months, although 1 patient lived at least seven years. Cooley and Hanske[404] described a case of acute lymphatic leukemia associated with lymphosarcoma.

Jordan[405] described the blood and tissues of an 18 year old girl who died of acute hemoblastic leukemia. The predominant cell resembled the small lymphocyte, which Jordan said represented a primitive cell type. This is the type of cell called by others a myeloblast, micromyeloblast, primitive blast and lymphoidocyte. There was gross invasion or transformation of the bone marrow, spleen, lymph nodes and thymus, with infiltration into other organs.

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402. Reiter, B. R., and Freeman, J. I.: Plasma Cell Leukemia, Am. J. M. Sc. **193**:38, 1937.

403. Isaacs, R.: Lymphosarcoma Cell Leukemia, Ann. Int. Med. **11**:657, 1937.

404. Cooley, L. E., and Hanske, E. A.: Acute Lymphatic Leukemia, J. Iowa M. Soc. **27**:535, 1937.

405. Jordan, H. E.: Hemoblastic Leukemia: Study of a Case, Arch. Path. **23**:653 (May) 1937.

Isaacs and Sturgis [406] studied 33 patients with monocytic leukemia. Of these, 70 per cent were males. The ages ranged from 5 to 78 years, with 59 per cent of the patients over 50. Acute and chronic forms were noted, with one to three relapses and remissions. In 1 case monocytic chloroma developed. The symptoms and signs in order of frequency were: weakness, 100 per cent; clinical splenomegaly, 82 per cent (8 patients who came to autopsy showed splenomegaly); fever, 82 per cent; loss of weight, 77 per cent; oral lesions (cheek, gums and pharynx), 73 per cent; pain, 64 per cent; hepatomegaly, 59 per cent; albuminuria at some stage, 50 per cent; purpura, 41 per cent; enlargement of the cervical glands (usually mild), 41 per cent; cutaneous lesions (other than purpura), 36 per cent, and epistaxis, 36 per cent. Characteristic changes were noted in the blood. Blood transfusion and arsenic gave temporary symptomatic remissions; irradiation was not efficient.

Osgood [407] reported data on 6 cases of monocytic leukemia and tabulated material for 127 cases reported in the literature. The clinical features were summarized as follows: an acute course, an unusual tendency toward swelling of the gums and the frequent association of fever, stomatitis and hemorrhages. The hematologic characteristics were the appearance of "promonocytes" in the blood and monoblasts and "promonocytes" in the sternal marrow. A specific cutaneous lesion was described. Wainright and Duff [408] published a detailed study of a case of acute monocytic leukemia in a 40 year old woman, with both myeloid and monocytic response.

Kandel [409] found reports of 175 cases of chloroma in the literature and noted that in most of the recent cases the chloroma had been classed as myeloid instead of lymphatic. It was postulated that chloroma is simply a variant of myelogenous leukemia in which the myeloblast develops into an invasive neoplasm.

Roehm, Riker and Olsen [410] described the occurrence of chloroma in a girl aged 13 years. The blood was aleukemic until nine days before death, and no abnormal leukocytes were noted in the blood stream. Profound anemia was present. The tumor cell, at autopsy, showed a

406. Isaacs, R., and Sturgis, C. C.: Types of Monocytic Leukemia, Tr. A. Am. Physicians **51**:40, 1936.

407. Osgood, E. E.: Monocytic Leukemia: Report of Six Cases and Review of One Hundred and Twenty-Seven Cases, Arch. Int. Med. **59**:931 (June) 1937.

408. Wainright, C. W., and Duff, G. L.: Monocytic Leukemia, Bull. Johns Hopkins Hosp. **58**:267, 1936.

409. Kandel, E. V.: Chloroma: Review of the Literature from 1926 to 1936 and Report of Three Cases, Arch. Int. Med. **59**:691 (April) 1937.

410. Roehm, H. R.; Riker, A., and Olsen, R. E.: Chloroma: Report of a Case, Ann. Int. Med. **10**:1054, 1937.

negative reaction for oxidase. There was extensive involvement of the cranium and viscera. The authors concluded that the green pigmentation was due to phagocytosis of blood in the obstructed capillaries by endothelial cells.

Forkner, Teng, Ch'u and Cochran [411] reported the fifth case of acute eosinophilocytic leukemia recorded in the literature. The average age of onset is 35.5 years (17 to 45) with a duration of twelve days to three months. The authors found that significant enlargement of lymph nodes was more common in this type than in other forms of myelogenous leukemia and that gross immaturity of the cells was not so marked.

*Pathology and Pathologic Physiology.*—Beltrametti, Rettanni and Bascapè [412] concluded that the anemia of leukemia is hemolytic and is a function of the hyperactivity of the spleen. In 12 cases (myelogenous and lymphatic leukemia) they noted a reduction in the number of leukocytes after irradiation, with an increase in the number of red blood cells, a lessening of the dispersion in the size of the red blood cells and a decrease in the evidence of destruction of hemoglobin.

Allen and Dickey [413] studied the secretion of polymorphonuclear neutrophils into the saliva in 10 cases of chronic myelogenous leukemia before and after roentgen therapy. An increase in the number of cells in the saliva follows maturation of myelocytes into forms capable of leukopedesis. The authors said they favored the view that irradiation increases the degree of maturation of the cells, although under certain circumstances it may cause the death of some of the abnormal forms. Irradiation may lower the blood stream and gastrointestinal threshold for leukopedesis.

Strumia and Boerner [414] studied the phagocytic activity of leukemic cells toward Staphylococcus aureus haemolyticus in vitro. None of the cells of the lymphocyte series showed phagocytic activity. In myelogenous leukemia, hemocytoblasts and myeloblasts showed but slight or doubtful phagocytic activity, but metamyelocytes, rod nuclear cells and adult neutrophils showed active phagocytosis. Türk cells showed no phagocytic activity. Monoblasts showed slight activity; hemohistioblastic cells showed strong phagocytic activity. The lymphoid cells of

411. Forkner, C. E.; Teng, C. T.; Ch'u, Y-C., and Cochran, W.: Eosinophilocytic or Eosinophilic Myelogenous Leukemia, Chinese M. J. **51**:609, 1937.

412. Beltrametti, L.; Rettanni, G., and Bascapè, A.: L'anemia nelle leucemie, Haematologica **18**:337, 1937.

413. Allen, K. D. A., and Dickey, L.: The Saliva Cell Count in Myelogenous Leukemia, Am. J. Roentgenol. **38**:57, 1937.

414. Strumia, M. M., and Boerner, F.: Phagocytic Activity of Circulating Cells in the Various Types of Leukemia, Am. J. Path. **13**:335, 1937.

infectious mononucleosis showed no phagocytosis. Eosinophils showed activity but less than that of the neutrophils or monocytes. Rieder's cells showed slight but definite activity.

Benians [415] noted that a gel was formed when congo red was mixed with leukemic blood.

In leukemia, Ishikawa [416] found that $p_H$ values for leukocytes were often abnormally high, above the normal of 12.5 to 17.5 (aerobic) and 11 to 12 (anaerobic).

The nucleus of myeloblasts in leukemia, Ishikawa [417] found, had a $p_H$ of 6.5 and the cytoplasm a $p_H$ of 6.4. This was more acid than the neutrophilic leukocytes of healthy men (nucleus $p_H$, 6.7; cytoplasm $p_H$, 6.6; granules, 7.1). While lymphocytes and monocytes had an acid reaction, eosinophilic granules were alkaline ($p_H$, 7.18).

Bossa [418] noted that leukemic leukocytes, especially of the lymphatic type, have the power of dehydrogenating fatty acids, with the production of keto acids (acetic). Bossa [419] found that the cells in cases of chronic myelogenous leukemia have a higher glycolytic rate than those in cases of lymphatic leukemia. The metabolism of the myeloid cells resembles that of neoplastic tissue, and that of the lymphoid series is more like that of embryonic cells.

The cells of the bone marrow, lymph nodes and circulating blood of patients with lymphatic leukemia were found by Look [420] to be without proteolytic action, whereas the marrow and lymph nodes of patients with myelogenous leukemia showed a strong digestive action. Stephens and Hawley [421] found unusually high values for reduced cevitamic acid in the whole blood of patients with leukemia, owing to the preponderance of leukocytes. Oszacki and Kurzweil [422] noted an alkalosis of the blood ($p_H$, above 7.36) of patients with leukemia, similar to the condition of the blood of patients with neoplastic disease.

415. Benians, T. H. C.: Observations on the Action of Congo Red on Normal and Leucemic Blood, J. Lab. & Clin. Med. **22**:1246, 1937.

416. Ishikawa, A.: The Oxidation Reduction Potential of Leukocytes (Measured with the Micromanipulator), Ztschr. f. klin. path. Hämatol. **4**:403, 1935.

417. Ishikawa, A.: The Hydrogen-Ion Concentration of Leukocytes (Determined by Micromanipulators), Ztschr. f. klin. path. Hämatol. **4**:305, 1935.

418. Bossa, G.: Sul potere deidrogenativo dei leucociti leucemici per gli acidi grassi, Riforma med. **53**:1545, 1937.

419. Bossa, G.: Sul metabolismo dei leucociti leucemici, Haematologica **18**:652, 1937.

420. Look, W.: Proteolysen-und Hemmungsversuche bei Agranulocytose-und Leukämieerkrankungen, Deutsches Arch. f. klin. Med. **178**:559, 1936.

421. Stephens, D. J., and Hawley, E. E.: Partition of Reduced Ascorbic Acid in Blood, J. Biol. Chem. **115**:653, 1936.

422. Oszacki, A., and Kurzweil, R.: Alkalose des Blutes bei Neoplasmen und ihre diagnostische und pathogenetische Bedeutung, Biochem. Ztschr. **289**:234, 1937.

Watson [423] found that the fecal excretion of urobilinogen was increased above the normal of 40 to 200 mg. per day in cases of pernicious anemia, Hodgkin's disease and leukemia.

Fiessinger and Laur [424] described the presence of round cytoplasmic particles, 4 to 8 microns in diameter, in the blood of patients with chronic lymphatic or myelogenous leukemia. They are probably artefacts, secondary to abnormal cytoplasmic fragility of the leukemic cells. Liberti [425] concluded that the nuclear shadows seen in blood films in cases of acute lymphatic leukemia are artefacts. Yaguda,[426] in noting the characteristic "patterns" in the cell types of the marrow in the different types of leukemia, pointed out the diagnostic importance of studies of the bone marrow, especially in the aleukemic states.

*Leukemia in Animals.*—In irradiated and nonirradiated mice inoculation with tumor cells of myeloid leukemia produced proliferation of the inoculated cells in the spleen, liver, lymph nodes and kidney and leukemic transformation of the marrow, with discharge of immature cells into the blood stream. From these experiments Rask-Nielsen and Rask-Nielsen [427] postulated that in mammalian leukemia an agent is present which causes a proliferation of the cells of the marrow.

Greppin [428] noted that bile neutralized the virus of fowl leukemia but that the inactivated virus did not produce immunity. It was possible to produce some degree of immunity with virus attenuated by heat, but no antibodies (complement deviation) could be demonstrated in the blood.

Magat and Magat [429] found that after the injection of lecithin perhydrite into leukemic chickens, there were spectroscopic differences from the blood of normal chickens receiving the same injection or from those with avian plague, diphtheria or acute anemia. The reagent was more toxic in leukemic chickens than in the others.

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423. Watson, C. J.: Studies of Urobilinogen: Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of Liver or Biliary Tract, Arch. Int. Med. **59**:196 (Feb.) 1937.

424. Fiessinger, N., and Laur, C. M.: Sur un corpusculin du sang des leucémies, Ann. de méd. **40**:212, 1936.

425. Liberti, R.: Le ombre nucleari nella linfoadenia leucemica acuta, Haematologica **18**:599, 1937.

426. Yaguda, A.: The Bone Marrow in Leukemia, J. M. Soc. New Jersey **33**:705, 1936.

427. Rask-Nielsen, H. C., and Rask-Nielsen, R.: Further Investigations on a Transmissible Myeloid Leukosis in White Mice, Acta path. et microbiol. Scandinav. **13**:244, 1936.

428. Greppin, J.: Les phénomènes d'immunite dans la leucémie transmissible des poules, Bull. Assoc. franç. p. l'étude du cancer **26**:232, 1937.

429. Magat, I., and Magat, M.: Recherches spectroscopiques sur le sang de poules leucémiques, Bull. Assoc. franç. p. l'étude du cancer **26**:259, 1937.

Storti and de Filippi [430] concluded that the reticuloendothelial system of the host does not take part in the development of leukemia in fowls after inoculation.

Using virus of chicken sarcoma, leukosis and osteochondrosarcoma, Furth and Breedis [431] found that viruses multiply in vitro only in the presence of cells on which they confer neoplastic properties. A single virus may stimulate both primitive blood cells and fibroblast-like cells. Leukemic myeoblasts of chickens remained viable in liquid cultures and were capable of producing leukosis when inoculated into chickens after thirty days. Viruses retained their characteristics during observation for from three to five years.

Furth, Kahn and Breedis [432] were able to transmit a type of mouse leukemia by the intravenous injection of single living leukemic cells. Injured cells or noncellular material was not effective in transmitting the disease. These experiments suggest that generalized leukemia may arise from a single focus, as opposed to the concept of multicentric origin.

Barnes and Furth [433] were able to transmit leukemia (atypical cell type) from one mouse to another of the same group or to unrelated mice if the latter had received massive and repeated doses of roentgen rays. Transmission failed when cell-free material was used or when the cells had been frozen rapidly to minus 30 C. When frozen slowly to minus 70 C. for thirty minutes or when kept at this temperature for thirty-two days, the cells were able to transmit the disease, possibly because some cells escaped uninjured. Sarcoma tissue of mice can be frozen to minus 70 C. and preserved for at least fifty-six days without inactivation (Breedis, Barnes and Furth [434]).

*Treatment.*—Sgalitzer [166] found that "total irradiation" was effective during the first two years in myelogenous leukemia but that in the later stages it had to be combined with local irradiation over the splenic area. In using the method in lymphatic leukemia, local treatment over

430. Storti, E., and de Filippi, P.: Das Verhalten des reticulohistiocytären Systems bei der Histogenese der übertragbaren Hühnerleukämie, Folia haemat. **58**:20, 1937.

431. Furth, J., and Breedis, C.: Attempts at Cultivation of the Viruses Producing Leukosis in Fowls, Arch. Path. **24**:281 (Sept.) 1937.

432. Furth, J.; Kahn, M. C., and Breedis, C.: The Transmission of Leukemia of Mice with a Single Cell, Am. J. Cancer **31**:276, 1937.

433. Barnes, W. A., and Furth, J.: Transmissable Leukemia in Mice with Atypical Cells Resembling Megakaryocytes, Am. J. Cancer **30**:75, 1937.

434. Breedis, C.; Barnes, W. A., and Furth, J.: Effect of Rate of Freezing on Transmitting Agent of Neoplasms of Mice, Proc. Soc. Exper. Biol. & Med. **36**:220, 1937.

the spleen and lymph nodes was necessary. This method did not influence the final outcome of the disease, although the course may have been somewhat milder than with the older methods.

Hunter [435] said he preferred high voltage roentgen therapy for chronic myelogenous leukemia rather than solution of potassium arsenite U. S. P. For aleukemic myelogenous leukemia he suggested that high voltage therapy to the spleen is worthy of a trial. In acute myeloblastic leukemia he found that all specific treatment was futile. Roentgen therapy made "the patient worse," and the use of blood transfusions and arsenic preparations should be discouraged, he said, because neither agent produces, with any consistency, even temporary benefit.

Parsons [436] reported excellent results in chronic leukemia with splenomegaly with the use of radium. Daily applications for three fifteen hour periods of 250 to 300 mg. of radium, screened with 2 mm. of lead, were made usually over the spleen once a year. Unpleasant reactions were less severe than after roentgen therapy.

Stephens [437] reported the production of hemopoietic and symptomatic remissions in a case of chronic myelogenous leukemia with arsenic and in another with irradiation. In the latter case, therapy was followed by a marked increase in excretion of nitrogen, but there was no change in the nitrogen balance in the former case.

Eley [438] found placental extract to be of use in stopping the hemorrhages in leukemia.

The blood of a patient with chronic myelogenous leukemia was used by Bock [439] to treat agranulocytosis. Fourteen transfusions were used with successful results. The withdrawal of the blood from the leukemic patient, with replacement with normal blood, was not followed by any harmful sequelae, and the author said it may even have been beneficial.

In the course of the arsenic treatment of chronic myelogenous leukemia, symptoms of arsenic poisoning may develop. Kandel and LeRoy [440] noted herpes zoster, cirrhosis, keratosis, polyneuritis, erythema, portal fibrosis and ascites. Some patients showed moist rales

435. Hunter, F. T.: The Leukemias: Their Diagnosis, Prognosis and Treatment, M. Clin. North America **21**:349, 1937.

436. Parsons, C. G.: Radium in Treatment of Leukemia, Brit. J. Radiol. **10**:573, 1937.

437. Stephens, D. J.: Chronic Myelogenous Leukemia: Observations Before and During Remissions Induced by Solution of Potassium Arsenite and by Roentgen Therapy with Particular Reference to Bone Marrow, Am. J. M. Sc. **194**:25, 1937.

438. Eley, R. C.: The Clinical Application of Coagulant Substance Obtained from Human Placenta, J. Michigan State M. Soc. **36**:377, 1937.

439. Bock, H. E.: Die Behandlung der Agranulozytose, Fortschr. d. Therap. **13**:537, 1937.

440. Kandel, E. V., and Leroy, G. V.: Chronic Arsenical Poisoning During Treatment of Chronic Myeloid Leukemia, Arch. Int. Med. **60**:846 (Nov.) 1937.

and a chronic cough. The symptoms of conjunctival and nasal congestion and of gastrointestinal disorders may be relatively late features compared with the others in patients who show some degree of toleration for the drug. When keratoses appear the use of arsenic must be discontinued temporarily and cautiously resumed after a rest period. Occasionally it is necessary to resort to roentgen therapy instead. Ordinarily it is well to wait with arsenic therapy until the postirradiation decline in the number of leukocytes has reached its lowest point. Twenty-one day cycles of arsenic, interspersed with twenty-one day rest periods were recommended.

Heinild and Schiødt [441] suggested the use of cevitamic acid in acute myeloblastic leukemia and in the chronic lymphatic form. They said they felt that better results were obtained (decrease in leukocyte count and cessation of hemorrhage) when this treatment supplemented roentgen therapy. The results were less marked in chronic myelogenous leukemia.

### BONE MARROW

With the increased study of bone marrow, the literature on the subject is becoming more involved. The sternal puncture method appears popular, but it is evident that quantitative data must be viewed with caution, as in some cases "pure" marrow is obtained, whereas in others a weak suspension of some marrow cells in blood is aspirated.

Details of the sternal puncture method of studying bone marrow were reviewed by Vogel, Erf and Rosenthal.[442] They described the appearance of the cells found in health and in disease.

Kirschbaum and Downey [443] found that the tissue section is the best method for the study of orientation in bone marrow, but the dry imprint method offers many advantages both for study of the cellular structure and for ease of preparation. Dameshek, Henstell and Valentine [444] said they preferred the biopsy to the puncture method, but the latter has the advantage of greater technical simplicity.

Stasney and Higgins [445] compared the cellular content of the bone marrow of the ribs and that of the proximal portion and of the middle

441. Heinild, S., and Schiødt, E.: Remission During the Course of Leukemia Treated with Cevitamic Acid, Ugesk. f. læger **98**:1135, 1936.

442. Vogel, P.; Erf, L. A., and Rosenthal, N.: Hematological Observations on Bone Marrow Obtained by Sternal Puncture, Am. J. Clin. Path. **7**:436, 1937.

443. Kirschbaum, A., and Downey, H.: A Comparison of Some of the Methods Used in Studies of Hemopoietic Tissues, Anat. Rec. **68**:227, 1937.

444. Dameshek, W.; Henstell, H. H., and Valentine, E. H.: The Comparative Value and the Limitations of the Trephine and Puncture Methods for Biopsy of the Sternal Marrow, Ann. Int. Med. **11**:801, 1937.

445. Stasney, J., and Higgins, G. M.: A Quantitative Cytologic Study of the Bone Marrow of the Adult Dog, Am. J. M. Sc. **193**:462, 1937.

portion of the femurs of 35 dogs, using imprint preparations. A remarkable similarity was noted in all the regions studied, leading to the conclusion that a uniform mechanism regulates hemopoiesis in different portions of the widely distributed marrow. The authors concluded that "the appraisal of the marrow of any one region will reveal what the trend of its cellular changes is elsewhere in the body."

Helpap [446] criticized the sternal puncture method on the basis that bone marrow is not homogeneous and that samples taken from one part of a bone differ from those taken from another part. He studied the sternal marrow of 32 patients who died as a result of diseases other than blood dyscrasias and found that 22 showed a homogeneous marrow. He found that the marrow of the long bones may differ from that of the sternum.

Isaacs [447] studied bone marrow obtained for biopsy and autopsy. The cells of the sternal bone marrow of 152 patients with various pathologic conditions and of 11 normal persons were enumerated from measured suspensions in serum. He found a great variation in the number and in the relative predominance of stages in the marrow, depending on the physiologic state of the individual at the moment the specimen was taken. Normally there are from 900,000 to 1,000,000 nucleated cells of all types per cubic millimeter. Of these, $23.1 \pm 8$ per cent are primitive blasts (erythroblasts and leukoblasts); $3 \pm 1$ per cent, megaloblasts; $7.2 \pm 2.5$ per cent, basophilic normoblasts, and $12 \pm 7$ per cent, eosinophilic normoblasts. In aplastic and hypoplastic anemia (nephropathy) the stage at which inhibition of growth is noted is the primitive blast stage; in pernicious anemia, cirrhosis of the liver and most macrocytic anemias, at the megaloblast stage, and in leukemia and in infection, at the normoblast stage.

The normal myelogram from the blood-diluted material aspirated from the sternum was reported by Mallarmé [448] as: polymorphonuclear neutrophils, 32.5 per cent; polymorphonuclear eosinophils, 2 per cent; polymorphonuclear basophils, 0.04 per cent; metamyelocytic neutrophils, 12 per cent; metamyelocytic eosinophils, 0.5 per cent; promyelocytes, 1.5 per cent; leukoblasts, 2.5 per cent; proerythroblasts and basophilic erythroblasts, 6 per cent; polychromatic and orthochromatic erythroblasts, 10 per cent; megaloblasts and promegaloblasts, 0; lymphocytes and mononuclear cells, 9.5 per cent; monocytes and reticuloendothelial cells, 2.5 per cent; plasmocytes and irritation cells, 0.9 per cent, and megakaryocytes, 0.06 per cent. The granulocyte-erythroblast ratio is

446. Helpap, K.: Zur Kritik der Sternalpunktion, Klin. Wchnschr. **16**:558, 1937.

447. Isaacs, R.: The Bone Marrow in Anemia:: The Red Blood Cells, Am. J. M. Sc. **193**:181, 1937.

448. Mallarmé, J.: Le myélogramme normal et pathologique, Sang **11**:804, 1937.

4.4. In pernicious anemia megaloblasts appear in the marrow, while in cryptogenic hypochromic anemia, macroblasts are present and the marrow is hyperplastic. Secondary anemias are characterized by normoblastosis; in polycythemia, by hypererythroblastosis and a megakaryocytosis; in leukemia, by leukoblastosis; in agranulocytoses of different types, by aplasia or hypoplasia of the granulocytes, with or without change in the other elements; in cancerous conditions, by hyperplasia of neoplastic tissue, and in Hodgkin's disease, by an increase in plasmocytes, monocytes, eosinophils and large endothelial cells.

In bone marrow of patients with Bright's disease Alexeieff [449] found a feeble erythroblastic regeneration, and the normal normoblast-granulocyte ratio of 1:5 was changed to 1:10. For 16 patients the erythrocyte counts of the peripheral blood varied from 2,200,000 to 4,950,000 per cubic millimeter and the leukocytes from 4,000 to 9,600. Alexeieff attributed the anemia to intoxication of the bone marrow with nitrogenous products, proportional to the duration of the disease but not the degree of azotemia. Leukocytosis (mercury bichloride poisoning) is an evidence of bone marrow regeneration. Hemorrhage is not due to thrombopenia, and the megakaryocytes and platelets are not affected. The variations in the nonprotein nitrogen content of the blood and of the bone marrow are comparable. In mercury bichloride poisoning in man and dogs the nonprotein nitrogen content of the marrow is elevated above that of the blood, differing in this respect from most of the other nephritides.

Domarus [450] cited 2 cases in which conclusions drawn from sternal puncture material were exactly opposed to the actual condition in the marrow. In the first case the diagnosis was active regeneration, when in reality the bone marrow was aplastic; in the second case a false diagnosis of aplastic anemia was made.

Kingery, Osgood and Illge [451] found sternal puncture a useful method in the diagnosis of leukemia cutis and in the differentiation of the lymphoblastoma. Weller [452] also found this technic useful. He used a spinal puncture needle, 18 gage and 3 inches (7.6 cm.) long, and withdrew a bit of marrow tissue, from which films were made.

449. Alexeieff, G.: La moelle osseuse des brightiques: Contribution sur l'étude de l'hématopoïèse et définition de l'azote non protéique dans la moelle osseuse des brightiques, Sang **11**:972, 1937.

450. von Domarus, A.: Ueber Irrtumer bei Auswertung der Sternalpunktion, Klin. Wchnschr. **16**:557, 1937.

451. Kingery, L. B.; Osgood, E. F., and Illge, A. H.: Sternal Puncture: A Diagnostic Aid in Leukaemia Cutis; a Possible Aid in Differentiating the Lymphoblastomas, Arch. Dermat. & Syph. **35**:910 (May) 1937.

452. Weller, G. L., Jr.: Bone Marrow Findings in the Diagnosis of Certain Blood Dyscrasias, M. Ann. District of Columbia **6**:253, 1937.

Osgood and Brownlee [453] developed a method of tissue culture for the study of bone marrow aspirated by sternal puncture. The material is grown in a synthetic saline solution containing dextrose. Other substances were added. The number of mitotic figures increased from forty to sixty times the number in the original marrow. With this method Osgood [454] found that polymorphonuclear neutrophils survived in the solution for sixty-one (forty-eight to ninety) hours; eosinophils, eight to twelve days, and basophils, twelve to fifteen days.

In vitro studies of human bone marrow were made by Weitzmann and Posern.[455]

Dameshek and Valentine [37] studied the sternal bone marrow of 20 patients with pernicious anemia at various stages of the disease. Tissues fixed in Zenker's solution (prepared according to the original formula, with acetic acid) and direct films were used, the latter being more valuable for cytologic data. The earlier work of Isaacs [456] was confirmed. The changes in the bone marrow were those of panmyelophthisis rather than a disease of red blood cells only.

In cases of tuberculosis Engelbreth-Holm [457] noted that splenomegaly, anemia and leukopenia developed because of a restriction of the maturing or delivering of the cells from the bone marrow and not from a decrease in cell production.

Lorando [458] found sternal puncture of value in the diagnosis of leishmaniasis. He noted that splenic puncture was not without danger. Giraud and Gaubert [459] said they preferred tibial puncture, especially for children. In kala-azar a positive diagnosis was made in 15 of 22 cases by means of this method. In 7 cases tibial puncture gave "nega-

453. Osgood, E. E., and Brownlee, I. E.: Culture of Human Marrow: Details of a Simple Method, J. A. M. A. **108**:1793 (May 22) 1937.

454. Osgood, E. E.: Culture of Human Marrow: Length of Life of the Neutrophils, Eosinophils, and Basophils of Normal Blood as Determined by Comparative Cultures of Blood and Sternal Marrow from Healthy Persons, J.A.M.A. **109**:933 (Sept. 18) 1937.

455. Weitzmann, G., and Posern, E.: Ueber das Wachstum menschlichen Knochenmarks in vitro, Virchows Arch. f. path. Anat. **299**:458, 1937.

456. Isaacs, R.: The Bone Marrow Changes (Quantitative) in Patients with Pernicious Anemia During the Period of "Reticulocyte Response," Tr. A. Am. Physicians **50**:249, 1935.

457. Engelbreth-Holm, J.: Tuberculous Splenomegaly and Splenogenic Inhibition of Bone Marrow Function, Bibliot. f. læger **129**:17, 1937.

458. Lorando, N.: La ponction sternale, méthode de choix pour la recherche des leishmanies, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:314, 1937.

459. Giraud, P., and Gaubert: Valeur de la ponction de la moelle osseuse pour le diagnostic du kala-azar méditerranéen (d'après les résultats de 22 ponctions du tibia), Bull. et mém. Soc. méd. d. hôp. de Paris **53**:336, 1937.

tive" results, while splenic puncture gave positive results. In 1 case splenic puncture gave a negative result and tibial aspiration a positive result.

Huddleson and Munger [460] studied the phagocytic activity of the cells of the marrow aspirated from the cavity of the femur of normal guinea pigs and of those immunized to Brucella and of cells from a patient with chronic myelogenous leukemia. While the cells from normal marrow did not ingest the bacteria mixed with them, cells or serum from an immune animal stimulated active phagocytosis. Leukemic cells did not phagocytose bacteria, but when human serum containing immune opsonins was added, the mature polymorphonuclear neutrophils and the stab forms ingested bacteria, although the cells of younger stages were inactive.

Brewer [461] found that bone marrow had a high content of the potassium isotope.[41]

In tissue cultures of spleen and of bone marrow Yagi [462] noted inhibition of growth when estrogenic substance was added, but the growth was stimulated when androgen was used. The reverse was true for certain other tissues. Corn oil and olive oil stimulated the growth of hemopoietic organs to the greatest extent of the ten vegetable oils used, the next most effective being oils of rapeseed, sesame and camellia.

In cultures of bone marrow Larionov [463] found that toluene and xylene were more strongly toxic than benzene. Ether and acetone killed the bone marrow cells only in high concentration. Benzene was toxic to leukocytes in vitro.

### HEMATOLOGIC TECHNIC

Erythrocyte and hemoglobin values for newborn infants were determined by Andersen and Ortmann.[464] Wide variations among presumably normal subjects were found. In general, the blood picture was characterized by macrocytosis and a high color index. They suggested the usefulness of determining the total quantity of blood in the newborn.

460. Huddleson, I. F., and Munger, M.: Phagocytic Activity of Bone Marrow Cells, Proc. Soc. Exper. Biol. & Med. **35**:27, 1937.

461. Brewer, A. K.: Abundance Ratio of the Isotopes of Potassium in Animal Tissues, J. Am. Chem. Soc. **59**:869, 1937.

462. Yagi, M.: Ueber die Einwirkungen des Ovahormons und des Enarmons auf die Entwicklung der Organgewebe des Kaninchens in Vitro gezüchtet, Sei-I-Kai M. J. (Abstr. Sect.) **56**:14, 1937.

463. Larionov, L. T.: Weitere Studien über die Wirkung der aromatischen Kohlenwasserstoffe und anderer Narkotika auf die Gewebekulturen, Arch. f. exper. Zellforsch. **19**:16, 1936.

464. Andersen, B., and Ortmann, G.: On the Number of Erythrocytes and the Content of Haemoglobin in the Blood of New-Born Children, Acta med. Scandinav. **93**:410, 1937.

Dhar [465] found the average hemoglobin value for native women of India to be 11.47 Gm. per hundred cubic centimeters, the erythrocyte count, 3,730,000 per cubic millimeter, the corrected color index 0.99, and the mean cell diameter 7 microns. His observations of lower normal blood values for Indian women than have been reported for the female population of Europe and America are in agreement with the findings of Napier and Das Gupta.[145] From his studies of the blood of normal Filipinos, Navarro [466] likewise found in both men and women slightly smaller erythrocytes, which contained less hemoglobin than those of healthy Americans. Biedenkopf [467] determined the hemoglobin and erythrocyte values, the mean corpuscular hemoglobin value, the diameter and area of the erythrocytes and the hemoglobin content per square micron of surface for 40 elderly men and women. He found that the sex differences in regard to red blood cell count and hemoglobin level were less marked in subjects over 60 years of age than in younger persons. Dulière and Adant [468] found that with an approximation of 5 to 6 per cent, they could deduce from the hematocrit percental volume of the erythrocytes the concentration of iron and of hemoglobin, the oxygen capacity and, in many cases, the red blood cell count. However, in comment, it should be pointed out that such deductions are valid only in the presence of erythrocytes of normal size and of a normal hemoglobin content. The mean corpuscular weight of the red blood cells of healthy men and women was determined by Isaacs, Bethell and Kyer.[469] For men the average value was found to be 73.6 micromicrograms; for women, 74.12 micromicrograms. There appeared to be no simple correlation between hemoglobin weight and total cell weight.

Weld and Woodward [470] suggested a modification of the method of determining the blood volume with congo red dye. Small amounts

465. Dhar, J.: Normal Hematological Standards in Indian Women, Folia haemat. **57**:78, 1937.

466. Navarro, R. J.: Hematology in Filipinos: Normal Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, and Mean Corpuscular Hemoglobin Concentration; the Various Normal Blood Indexes, J. Philippine Islands M. A. **17**:611, 1937.

467. Biedenkopf, H.: Das Blut des Menschen, mit neueren Methoden untersucht; absolute Hämoglobinbestimmungen Erythrozytenzählungen und Erythrozytenmessungen bei 40 alten Männern und Frauen zur Ermittlung des Hämoglobingehalts eines Erythrozyten und des Hämoglobins je $\mu^2$ Oberfläche des Erythrozyten, Ztschr. f. Biol. **97**:445, 1936.

468. Dulière, W. L., and Adant, M.: Relation entre le volume globulaire et la concentration en fer: Signification du chiffre de l'hématocrite, Bull. Soc. chim. biol. **18**:1589, 1936.

469. Isaacs, R.; Bethell, F. H., and Kyer, J. L.: The Weight of Red Blood Cells in Health and Anemia, Univ. Hosp. Bull., Ann Arbor **3**:85, 1937.

470. Weld, C. B., and Woodward, H. E.: Note on Blood Volume Determinations, J. Lab. & Clin. Med. **22**:410, 1937.

of hydrogen peroxide are added to both the standard and the unknown solution, thus bleaching out hemoglobin resulting from hemolysis. The procedure is especially valuable in determinations of the blood volume of dogs, in which hemolysis is likely to be a troublesome factor.

The mean diameter of erythrocytes was determined by Schalm,[471] using different instruments for the measurement of diffraction rings. Most accurate determinations of the size of the red blood cells were obtained with Pijper's instrument, and by this method the normal mean diameter was found to be 7.8 microns. Values were reported for mean erythrocyte diameter in cases of hepatic disease and obstructive jaundice. Freerksen[472] found that the size of the red blood cells in health and in disease conditions is remarkably constant and that it depends on the size of the antecedent normoblasts. He concluded that changes in the size of the erythrocytes occurring in various diseases of the erythropoietic system must always be considered in conjunction with quantitative changes in the marrow.

Tocantins[473] reviewed the subject of the technologic study of blood platelets. He described many methods for the enumeration of platelets and their morphologic study. A technic was given for the study of platelets and megakaryocytes in sections of fixed tissue. The volumetric measurement of platelets was discussed, as well as methods for the isolation of platelets from the blood. He also described the preparation and testing of antiplatelet serum. He[474] found that the number of platelets in arterial and venous blood was significantly higher in winter than in spring but that no such difference occurred in cutaneous blood. In winter the platelet count was found to be highest in arterial blood, but counts made in spring on blood from the arteries, veins and cutaneous vessels were essentially the same. He found no statistically significant seasonal variations in red blood cell counts.

A technic for the determination of platelet volume was described by Olef.[475] The principle of the method depends on immediate dilution of the venous blood with a platelet-preserving solution, rapid isolation of platelets by centrifugation and measurement of volume by subsequent centrifugation of the suspension of platelets in a thrombocytocrit pipet. The mean total platelet volume for 31 normal adults was 0.33 volumes

471. Schalm, L.: Measurement of the Mean Diameter of Red Blood Cells, Nederl. tijdschr. v. geneesk. **81**:5786, 1937.

472. Freerksen, E.: Das Problem der Erythrocytengrösse—Eine anatomische Frage? Klin. Wchnschr. **16**:1238, 1937.

473. Tocantins, L. M.: Technical Methods for the Study of Blood Platelets. Arch. Path. **23**:850 (June) 1937.

474. Tocantins, L. M.: Seasonal Variations in the Number of Platelets in the Arterial, Venous and Cutaneous Blood in Man, Am. J. Physiol. **119**:439, 1937.

475. Olef, I.: Determination of Platelet Volume, J. Lab. & Clin. Med. **23**:166, 1937.

per cent, with a range of 0.26 to 0.44 per cent. The mean individual platelet volume for the group was 7.3 cubic microns. The author concluded that the determination of the volume of packed platelets is a useful hematologic procedure but that it should not be used as a substitute for platelet enumeration, because of a lack of absolute parallelism between the volume and the total count, attributable to variations in the fragility and in the size of the thrombocytes.

The usefulness of a simple test for the estimation of erythrocyte sedimentation was discussed by Bannick, Gregg and Guernsey.[476] They found a threefold application of the test to clinical problems: (1) detection of disease; (2) measurement of activity and progress of such diseases as tuberculosis, pelvic inflammatory conditions, acute cholecystitis, rheumatic fever, infectious arthritis, pneumonia and other thoracic infections and suppurations, Hodgkin's disease, acute febrile illnesses and acute coronary thrombosis, and (3) assistance in differential diagnosis. Brooks[477] and Dorfman and Brooks[478] described a new micropipet for measurement of the sedimentation rate and studied the effects of temperature, inclination of the tube and delay in carrying out the test after removal of the blood sample. Frimberger[479] found an inverse relation between the minimum sedimentation rate and the hemoglobin value, the erythrocyte count and the color index when these determinations were below normal levels. Extensive experimental and clinical studies of the sedimentation rate, made chiefly on patients with pulmonary tuberculosis, were reported by Carez and Wynants.[480] They concluded that both the time curve and the time required for the red blood cells to fall a given distance should be taken into consideration in determining the rate of sedimentation, and they presented a mathematical expression for the combined readings. Their article included a partial review of the literature. Volk[481] reported the results of 1,000 determinations of the sedimentation rate made for patients with pulmonary tuberculosis. The Cutler method was employed in this study. He found

476. Bannick, E. G.; Gregg, R. O., and Guernsey, C. M.: The Erythrocyte Sedimentation Rate: The Adequacy of a Single Test and Its Practical Application in Clinical Medicine, J.A.M.A. **109**:1257 (Oct. 16) 1937.

477. Brooks, C.: New Micropipet for Sedimentation Measurement, Am. J. M. Technol. **3**:1, 1937.

478. Dorfman, R. I., and Brooks, C.: The Accuracy of a New Technique for Measurement of Red Blood Corpuscle Sedimentation, J. Lab. & Clin. Med. **22**:510, 1937.

479. Frimberger, F.: Das Minimalsediment des Blutes und seine Beiziehungen zu Zahl und Hämoglobingehalt der Erythrocyten, Klin. Wchnschr. **16**:90, 1937.

480. Carez, C., and Wynants, J. H.: New Method of Reading Sedimentation Rate, Rev. de la tuberc. **3**:774, 1937.

481. Volk, R.: Red Cell Sedimentation in Pulmonary Tuberculosis, Am. Rev. Tuberc. **36**:567, 1937.

the test of especial value in measuring the activity of the disease in the presence of pneumothorax or thoracoplasty, roentgen findings frequently being limited to evidence of pulmonary collapse. Riseman and Brown [482] studied changes in the sedimentation rate of patients with angina pectoris and coronary thrombosis. They found a moderate increase in rate in the former condition and much more marked acceleration in the latter, especially between the fourth and the twelfth day after the attack. They concluded that for two weeks after an acute onset the sedimentation rate may offer valuable aid in differentiating between angina pectoris and coronary thrombosis. It is not useful in the prognosis of an acute attack but is helpful in measuring progress during recovery.

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482. Riseman, J. E. F., and Brown, M. G.: Sedimentation Rate in Angina Pectoris and Coronary Thrombosis, Am. J. M. Sc. **194**:392, 1937.

# News and Comment

**International Congress on Rheumatic Diseases.**—At the International Congress on Rheumatic Diseases held at the University of Oxford, March 28 to 31, 1938, Dr. Ralph Pemberton, of Philadelphia, was elected president, to succeed Dr. R. Fortescue Fox, of London, who did not wish to accept a new appointment as council member. At the urgent request of the members, the secretary and director of the International Advisory Bureau, Dr. J. van Breemen of Amsterdam, who had tendered his resignation, expressed his willingness to remain in office for the present. The other council members were re-elected. Prof. J. Rother, of Berlin, was given a seat on the council as representative for Germany.

A committee was appointed to collect statistics, to revise the by-laws and to reorganize the journal *Acta rheumatologica.*

The invitation of the American delegates to hold the next congress in New York in June 1940 was accepted. The official subjects to be discussed at that meeting will be (1) the role of infection in rheumatic diseases, (2) nutrition in rheumatism and (3) the social significance of orthopedic work in rheumatic diseases.

It was also resolved to hold a symposium on therapy in rheumatism and to furnish opportunities for the presentation of unscheduled papers.

**American Congress of Physical Therapy and American Occupational Therapy Association.**—The seventeenth annual scientific and clinical session of the American Congress of Physical Therapy will be held cooperatively with the twenty-second annual convention of the American Occupational Therapy Association, Sept. 12 to 15, 1938, at the Palmer House, Chicago. Preceding this session, from September 7 to 10, inclusive, the congress will conduct an intensive seminar on physical therapy for physicians and technicians. The program of the convention proper will include numerous special features, and a variety of papers and addresses, clinical conferences, round table talks and extensive scientific and technical exhibits are scheduled.

Information concerning the convention and the seminar may be obtained by addressing the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

# Book Reviews

**Textbook of Diagnostic Roentgenology.** By Lewis J. Friedman, M.D., Director, Roentgen-Ray Department of the Bellevue Hospital. Price, $10. Pp. 623, with 638 illustrations. New York: D. Appleton-Century Company, Inc., 1937.

This book consists of thirty-four chapters, which are divided among six clearly demarcated sections. In the first section the author considers certain of the fundamental principles of the physics of the roentgen ray, describes the technic of fluoroscopy and outlines standard methods for obtaining satisfactory roentgenograms. The succeeding sections of the volume are devoted, respectively, to the roentgenographic aspects of diseases of the osseous system, the respiratory system, the cardiovascular system, the alimentary tract and the genito-urinary tract, including in the latter field diseases of the uterus, adnexa and female pelvis and roentgenographic pelvimetry.

The book as a whole contains a wealth of sound and practical information. For the most part the descriptions of the various subjects under discussion are clear, and the illustrations are adequate; a few illustrations, to be sure, are poorly reproduced. There are occasional line drawings which are well described. There are concise, well written summaries describing the newer roentgenographic procedures, such as the diagnostic use of iodized oil, ventriculography, encephalography, myelography, bronchography, kymography, cholangiography, urography, salpingohysterography, and methods of visualization of the spleen and liver. These are especially interesting not only to the roentgenologist but also to the internist, because these newly developed methods are indicative of the trend this science has taken in recent years.

In each of the chapters many useful points of differential diagnosis are presented, and diseases of the various systems are discussed in a manner which is helpful to any one in practice. Thus the book is of interest to the general reader as well as to the specialist.

It is, of course, to be expected, because the book has attempted to cover so large a field, that many items would be briefly treated and some even omitted. No reference is made, for example, to the roentgenographic findings in cases of sprue and steatorrhea. Adenoma of the gallbladder is dismissed with one sentence. These gaps in a measure are compensated for by a well selected bibliography at the end of each chapter.

The allotment of space for the subject matter has been wisely handled. The book has been well written and is one that any physician can read with profit and find valuable as a work of reference. It is well adapted for teaching purposes. It clearly demonstrates the tremendous present-day value of roentgenography in the diagnosis of various diseases. On the whole, this new textbook can be heartily recommended.

**Pathology of the Central Nervous System.** By Cyril B. Courville, M.D., Professor of Neurology and Psychiatry, College of Medical Evangelists, and Director, Cajal Laboratory of Neuropathology, Los Angeles County Hospital. Price, $5.75. Pp. 344, with 200 illustrations. Mountain View, California: Pacific Press Publishing Association, 1937.

This new textbook has been written for medical students at their request and for this reason has been kept simple. Because of its simplicity it will appeal to many general readers, particularly those interested in the nervous system but a little fearful of its intricacies.

The author, being a pathologist, avoids as best he can the attachment of personal names to the different clinical syndromes that are encountered in the field of

clinical neurology. Rather, he wishes to have his students learn to make clinical diagnoses on a pathologicophysiologic basis, and he attempts to show how this may be done in a logical manner.

His method of approach is pleasant. He claims that for a proper understanding of diseases of the nervous system the life history of each lesion, as well as its peculiar predilections for certain regions of the brain or spinal cord, is of vital importance and that knowledge of the pathogenesis of the various diseases of the nervous system often gives a clue as to the nature of their early manifestations. He attempts to lay the necessary foundation for such a point of view by a painstaking clinicopathologic analysis of the material that has passed through his laboratory, comprising a series of fifteen thousand autopsies.

In this analysis especial emphasis is laid on the stage of development of the lesions under consideration which have been shown in his cases, on their gross morphologic character and on their ultimate effect on the nervous system. Thus, relatively little space has been given to a description of minute histologic alterations, and a great deal has been given to gross pathologic and clinical description.

The subject matter is divided in an orthodox manner. The congenital anomalies, the diseases of the intracranial blood vessels, the infectious diseases, traumas, the intoxications, the degenerative diseases of unknown origin, like multiple sclerosis, and the tumors, each receives appropriate discussion.

The entire volume makes interesting reading. It is well indexed, with a good bibliography for reference work. It is beautifully illustrated with photographs and easily comprehended diagrams. It contains many useful clinical aphorisms. On the whole, this new volume on the pathology of the central nervous system is well worth acquiring.

**Some Fundamental Aspects of the Cancer Problem: Symposium Sponsored by the Section on Medical Sciences of the American Association for the Advancement of Science.** Edited by Henry Baldwin Ward. Price, $2.50. Pp. 248, with illustrations and tables. New York: The Science Press, 1937.

In the last days of 1936 the Section on Medical Sciences of the American Association for the Advancement of Science held a symposium on cancer at Atlantic City, N. J. The papers which were presented have now been assembled in book form under the editorship of Dr. Ward. The result is an impressive volume.

The book is made up of thirty-one articles, short for the most part, well written and well illustrated with the necessary tables and graphs to make for clarity. Cancer is considered from four points of view: heredity, agents that may stimulate or inhibit tumorous growths, the metabolism of cancerous tissue and irradiation and, finally, by general discussion. The papers dealing with these subjects are grouped together as informatively as possible. Each paper is written by an authority in the particular field under discussion.

The student of cancer will be glad to have so complete and polished a record of this symposium. Especially, however, medical students and physicians should be encouraged to read this book. For if, as Dr. Dublin predicts, during the next twenty-five years in this country the present annual toll of 150,000 lives as a result of cancer is doubled, cancer and its problems must continue to be of increasing interest to all members of the profession. Here is an excellent opportunity for physicians and students to learn how cancer is at present being investigated and to gain an inkling of the new lines of attack that are likely to be developed in the immediate future.

**Der Blutdruck des Menschen.** By Eskil Kylin, M.D. Price, 24 marks. Pp. 322, with 22 illustrations. Dresden: Theodor Steinkopff, 1937.

This book represents 261 pages of discussion on the blood pressures of man, including not only the arterial but the capillary and the venous pressure as well. Methods for determinations of the pressure in each class of vessels are described,

criticized and evaluated. The physiology of the regulation of blood pressure is detailed. Central, reflex, and hormonal control are given adequate consideration. Normal regulation is followed by pathologic physiology, leading to a consideration of both hypertension and hypotension. Included are such special cases as the Cushing syndrome, diabetes, adrenal tumors, pregnancy, essential and postural hypotension and Addison's disease.

Although the work is highly colored by German thought and ideas, the literature reviewed is world wide, a fact well reflected in the text itself. One will find in it little regarding specific directions for the handling and treatment of the patient. However, it will supply the physician with much recent knowledge regarding normal and pathologic physiology, which is so essential to the proper understanding of the nature of blood pressure control and consequently to the rational management of the patient.

**Le eritremie.** By G. di Guglielmo. Pp. 23. Pavia: Tipografia Già Cooperativa, 1936.

This paper is an attempt to classify the proliferative disorders of the erythropoietic system logically. The preferred term for the group is erythremic myelosis. The subdivisions, in order of decreasing anaplasia of the erythropoietic tissue, are as follows:

1. Very acute erythremic myelosis of the newborn (erythroblastosis foetalis)
2. Acute erythremic myelosis (acute erythroblastic anemia)
3. Chronic erythremic myelosis (Cooley's erythroblastic anemia)
4. Chronic erythremic myelosis, Vaquez type (polycythaemia vera). Intergradations between these forms and leukemic myeloses of comparable severity are described and named. (In the discussion which followed the presentation of the paper the author suggested including this fourth form.)

The syndromes discussed appear to be more common in Italy than in this country. The discovery and the recognition of the rarer types, especially the leukemic and erythremic combinations, are praiseworthy, and the logical classification offered is a credit to Italian hematology.

**The Roentgenologist in Court.** By Samuel Wright Donaldson, M.D. Price, $4. Pp. 230. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

This is an interesting book. The author believes that most physicians know far too little regarding legal matters, and he here attempts to tell something of the mysteries of the law and how they may affect physicians.

The subject matter has been divided into fourteen chapters. These chapters deal with such broad legal topics as malpractice, testimony and contracts and have, as would be judged from the title of the volume, a good deal to say about the roentgenologist and his legal position.

The author has quoted a great number of cases to show how legal opinion regarding various phases of medical work has become established. So many legal case reports make the reading a little difficult for one unfamiliar with legal phraseology. However, the book as a whole makes an excellent work of reference. There is no doubt, as the author infers, that physicians are woefully ignorant of legal matters. This book at least puts them in the way of acquiring a modicum of medicolegal education.

**Investigations into the Epidemiology of Epidemic Dropsy.** By R. B. Lal, S. C. Roy and S. C. Ghosal. Pp. 97. Calcutta: Thacker, Spink & Co., 1937.

This paper, a reprinting of five articles from the *Indian Journal of Medical Research*, is a competent modern study of a disease of peculiar interest to public health officers. The syndrome of epidemic dropsy has been recognized in eastern India since 1877. There have been frequent outbreaks, resulting in as many as 1,575 deaths, although most of them have involved the relatively few inhabitants

of small Bengalese villages. Earlier epidemiologists attributed the outbreaks to bacterial toxins generated in infected rice. The present writers appear to have eliminated rice as the poisoning agent and have demonstrated convincingly that certain pressings of mustard oil (the chief food fat of the victims) are responsible for the disease. Unfortunately the nature of the toxic substance is not disclosed in this paper, but further researches are promised.

**Clinical Studies of Tributary Thrombosis in the Central Retinal Vein.** By Viggo A. Jensen. Copenhagen: Levin & Munksgaard, 1936.

This work offers a complete study of the vascular system of the eye as a preliminary to the main theme, tributary thrombosis of the central retinal vein.

The author attempts to prove that there is a system in the apparently irregular branching of the retinal vessels, and he feels that he has established certain typical variations in the known course of the vessels.

The second section of this treatise deals with clinical studies of cases of tributary thrombosis. The ophthalmoscopic picture is described and correlated with the anatomic studies reported in the first section of the work.

Studies of the visual fields in the course of the disease and many drawings illustrating the picture of the fundus in cases of tributary thrombosis accompany the text. The fifty-four patients studied were followed through to the ultimate conclusion.

**The Endocrines in Theory and Practice.** Republished from the British Medical Journal. Price, 9s. Pp. 278. London: H. K. Lewis & Co., Ltd., 1937.

This volume is a collection of papers reprinted from the *British Medical Journal* and designed to familiarize the reader with the present status of endocrinology. The subject is discussed from a practical standpoint, and theoretical considerations are eliminated so far as possible.

The pituitary body, the thyroid gland, the adrenal glands and the gonads are discussed at length. The thymus, the pineal body and the parathyroid glands receive somewhat less attention.

Clinical considerations of diagnosis and treatment are given a prominent place.

A difference in the British and in the American point of view is shown in certain places. This is particularly evident in the discussion of the etiology of goiter and in the treatment of hyperthyroidism.

The whole book is sound and conservative, and a place in the literature of endocrinology is well merited.

**Diseases of the Nervous System in Infancy, Childhood and Adolescence.** By Frank R. Ford, M.D. Price, $8.50. Pp. 953, with 107 illustrations, 14 charts and 14 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

As it is well printed and beautifully and profusely illustrated, one immediately has a sense of pleasure on opening this book. Dr. Ford has dealt with his subject thoroughly. Of special value are the discussions of the neurologic conditions of childhood. One wishes that he had devoted more space to these, since there is otherwise a good deal of material which is readily available in general medical and neurologic textbooks. Especially valuable are the references, conveniently placed after each section. The abstracts of individual cases make a difficult subject more vivid and comprehensible.

**La thrombose de l'artère bronchique, cause de dilatation bronchique chronique de l'adulte.** By J. M. Lemoine, M.D. Price, 30 francs. Pp. 189, with 27 illustrations. Paris: E. Le Francois, 1936.

In this brief monograph the author sustains the thesis that bronchial dilatation is due to thrombosis of the bronchial artery. While one may not agree with the conclusions, one must admit that a good deal of interesting material has been assembled.

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